HRPP HANDBOOK

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Section 1 - The Human Research Protection Program

Geisinger's Human Research Protection Program (HRPP) encompasses the entities that contribute to its mission to protect the rights and welfare of individuals who participate in human subjects' research.

Geisinger Human Research Protection Program Policy was established to ensure Geisinger's compliance with all federal, state, and institutional policies for the protection and oversight for all human subjects' research. This includes all human subjects research conducted by members of the Geisinger community, using Geisinger facilities or resources, or involving use or disclosure of identifiable private information created or maintained by Geisinger. The Human Research Protection Program (HRPP) is guided by the ethical principles of the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research entitled ***Ethical Principles and Guidelines for the Protection of Human Subjects of Research*** (the "Belmont Report") and performed in compliance with applicable federal and state law.

The Human Research Protection Program (HRPP) is an integrated system of the Institutional Review Board (IRB), Office of Research Compliance (ORC), Office of Sponsored Projects (OSP), other review units, oversight functions, and educational and quality assurance activities that together seek to assure the rights and welfare of human subjects participating in research and promote excellence in all aspects of human subjects research. The HRPP not only promotes compliance with relevant laws, regulations, and professional and ethical standards at all levels, it addresses the needs and concerns of researchers and enhances support of their endeavors.

The Geisinger HRPP Handbook provides information about the organization, scope, authority, and responsibilities associated with the Geisinger HRPP for the research community at Geisinger and its affiliates.

1.1 Organizations Covered by the Geisinger Human Research Protection Program (HRPP)

The HRPP exists to promote high quality, ethical research. The HRPP does this by serving as the advocate for the rights and welfare of persons who participate in human subjects' research conducted at Geisinger and all affiliate organizations for which there is an agreement to provide services related to the HRPP.

1.2 Goals and Objectives of the HRPP

*Geisinger has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, Research Participants, and the Institutional Review Board as appropriate. (**AAHRPP Element I.1.D**)*

Goals of the HRPP

The goal of the HRPP is to protect human research participants by ensuring that in all Geisinger research:

- The rights and welfare of human research participants are protected.
- Such research is guided by the ethical principles of respect for persons, beneficence, and justice as set forth in the Belmont Report, and is conducted with the highest level of expertise and integrity.
- Such research complies with applicable laws.

Objectives of the HRPP

The HRPP includes mechanisms to:

- Monitor, evaluate, and continually improve the protection of human research participants and dedicate resources sufficient to do so.
- Exercise oversight of human subject research protection.
- Educate investigators and research staff about their ethical responsibility to protect research participants.
- When appropriate, intervene in human subject research and respond directly to concerns of research participants.

HRPP Process

The HRPP includes policies and processes found within the HRPP Handbook, Guidance documents, and any other supporting documents governing human subjects research and the protection of participants. Geisinger's Institutional Official (IO) assures the protections of human subjects in accordance with our Federalwide Assurance through leadership of Geisinger's HRPP and appropriate delegation of responsibilities. The IO represents the institution named in the Federalwide Assurance.

1.3 Delegation of Responsibility for Geisinger HRPP Implementation

*Geisinger delegates responsibility for the Human Research Protection Program to an official with sufficient standing, authority, and independence to ensure implementation and maintenance of the program. (**AAHRPP Element I.1.B**)*

For the organizations covered by the HRPP, the Chief Executive Officer (CEO) of Geisinger delegates the primary responsibility for Geisinger's HRPP to the Institutional Official (IO) whose responsibility is to exercise appropriate administrative oversight to ensure that Geisinger's policies and procedures designed for protecting the rights and welfare of human participants are effectively applied in compliance with its Federalwide Assurance. This individual is responsible for ensuring that the HRPP functions effectively and that the institution is provided resources and support necessary to comply with all requirements applicable to research involving human subjects.

The HRPP Handbook is a dynamic document because the scientific developments, ethical issues, and regulatory circumstances that shape it are continuously evolving and improving. The Office of the Institutional Review Board (IRB) has been delegated to maintain policies and procedures and manage operations of Geisinger HRPP. The HRPP Handbook contains policies and written procedures reflecting the current practices of the IRB in conducting reviews and approvals of human research. The Director, IRB Operations and HRPP in consultation with IRB staff conduct regular reviews (i.e., at least annually), refines the HRPP Handbook and written procedures and makes recommendations for modifications or develops new policies and procedures as appropriate. The IO may approve modifications to any portion of the HRPP Handbook. The Director may approve modifications to the HRPP Handbook that relate to the day-

to-day review and operational functions of the IRB. The IRB staff is responsible for disseminating all modifications to the HRPP Handbook and incorporating them into the relevant educational programs (discussed in Section 4 - Knowledge of Human Research Protection Requirements).

1.4 Research Covered by the HRPP

Types of human subjects' research at Geisinger

*Geisinger has and follows written policies and procedures for determining when activities are overseen by the Human Research Protection Program as incorporated into the Policy Manual. The IRB on behalf of the HRPP will institute a continual process for reviewing and monitoring compliance with human subject research. (**AAHRPP Element I.1.A**)*

All human subjects research that involves Geisinger is covered by the HRPP.

The Geisinger Institutional Review Board has expertise to review and oversee both biomedical (research about normal or abnormal physiology and development, and studies primarily intended to evaluate the safety, efficacy, and usefulness of drugs, biologics, devices, medical products, procedures, or interventions) and behavioral, educational, and social science research. Human subjects research is covered by a Federalwide Assurance (FWA) as filed with the Office for Human Research Protections (OHRP).

The Federalwide Assurance (FWA) is the only type of assurance of compliance accepted and approved by OHRP for institutions engaged in non-exempt human subjects research conducted or supported by U.S. Department of Health and Human Services (HHS). Under an FWA, an institution commits to HHS that it will comply with the requirements set forth in 45 CFR part 46, as well as the Terms of Assurance.

Geisinger applies the HHS Final Rule (2018 Revised Common Rule) to all research, including FDA-regulated research when 2018 Revised Common Rule regulations are compatible. However, GIRB reserves the right to make exceptions for human subjects' research outside the scope of the FWA if determined by the IRB to be appropriate for the research. In all cases, these studies will be afforded protections commensurate with risk as determined by the IRB. Such research remains subject to relevant Geisinger IRB policies and review standards as described in the HRPP Handbook, related Guidance documents and Geisinger policies. If the federal support status of a study reviewed under such flexible provisions changes, it is the responsibility of the Principal Investigator to notify the IRB immediately via amendment/modification, so the research can be reviewed under the HHS Final Rule, 45 CFR 46.

Effective May 1, 2018, GIRB applied flexible provisions adapted from the *Final Revised Common Rule 45 CFR 46 Subpart A - Basic HHS policy of Protection of Human Research Subjects (January 18, 2017)* to research that was neither federally sponsored nor FDA-regulated, specifically:

- Adopted revised Exemption Categories 1-6 (See Guidance – *Exempt Review Categories*)
- Required "Limited Review" by IRB member as a condition for Exemption 2(iii) and 3(i)(C)
- Eliminated the continuing review requirement for most minimal risk research and required documentation of rationale for continuing review of research that otherwise would not require continuing review
- Expanded general requirements for informed consent, including organization of informed consent

so that key information is presented first and organized and presented in a way that facilitates comprehension (required for informed consents approved on or after May 1, 2018) (See *Guidance – Informed Consent – Required Elements.*)

The IRB evaluated all ongoing studies for transition to these flexible review provisions at the time of the study's continuing review occurring on or after May 1, 2018. All research that transitioned to these provisions since May 1, 2018, are considered transitioned to the HHS Final Rule (2018 Revised Common Rule) for the remainder of the research.

Effective January 21, 2019, Geisinger expanded application of the HHS Final Rule (2018 Revised Common Rule) to all research except FDA-regulated research. This applies to all research approved on or after January 21, 2019. The IRB evaluated all ongoing studies for transition to the HHS Final Rule (2018 Revised Common Rule) at the time of the study's continuing review occurring on or after January 21, 2019.

Geisinger (or its employees or agents) is engaged in human subjects research – as defined by being involved in one or more of the following activities (in accordance with the OHRP guidance, Engagement of Institutions in Human Subjects Research):

- Receiving an award through a grant, contract, or cooperative agreement directly from HHS or other federal agency for the non-exempt human subjects research.
- Intervening for research purposes with any human subjects of the research by performing invasive or noninvasive procedures.
- Intervening for research purposes with any human subject of the research by manipulating the environment.
- Interacting for research purposes with any human subject of theresearch.
- Obtaining the informed consent of human subjects for theresearch.
- Obtaining for research purposes identifiable private information or identifiable biological specimens from any source for the research.

The Office for Human Research Protections (OHRP) provides leadership in the protection of the rights, welfare, and wellbeing of subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS). OHRP helps ensure this by providing clarification and guidance, developing educational programs and materials, maintaining regulatory oversight, and providing advice on ethical and regulatory issues in biomedical and social-behavioral research.

Geisinger's policy for the protection of human participants is guided by ethical principles, Federal law, and institutional standards. The guiding ethical principles are embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Compliance with this policy provides protections for human participants as mandated by applicable laws, regulations, and standards of local, state and federal government agencies concerning the protection of human participants, including the U.S. Code of Federal Regulations (CFR):

Title 45 CFR 46, Protection of Human Subjects, U.S. Department of Health and Human Services (DHSS), OHRP and

- Title 21 CFR 50, 56, 312, 600 and 812 of the Food and Drug Administration (FDA)
    - An activity is covered by the HRPP when it meets the definition of human subject research as defined by

HHS, FDA and/or any other applicable state or local regulations, e.g., PA state regulations. Section 3.3 provides details for determining when studies meet the regulatory definitions of human subject research

Approvals Required Before Human Subject Research May Begin

IRB approval and contract execution (when applicable) are required before any research activities may begin. In addition, some protocol-specific situations require additional review and approval by other organization units or must meet their standards (see Sections 1.5 - Primary Officials, Administrative Individuals of the HRPP and 2.4 - Human Research Protection, Care of Participants, and Safety).

Definitions (HHS) (Common Rule)

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 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 part, the following activities are deemed not to be research:

(1) Scholarly and journalistic activities (*e.g.,* oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, which focus directly on the specific individuals about whom the information is collected.

(2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during an event or crisis that threatens public health (including natural or man-made disaster.

(3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.

(4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

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

(1) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or

(2) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

Definitions (FDA)

Research 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))

Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject might be either a healthy individual or a patient. For research involving medical devices a human subject is also an individual on whose specimen an investigational device is used.

- When medical device research involves in vitro diagnostics and unidentified tissue specimens, the FDA defines the unidentified tissue specimens as human subjects.

Definitions

Federally supported means that the research is supported by federal funding or other type of federal involvement. GIRB staff members rely upon the information provided by the researcher, except when the provided information is inconsistent or ambiguous about federal support. If there is no indication of federal support, the researcher is not asked for confirmation that there is no federal support. "Federal support" includes any of the following:

- Funding from any federal agency. This means:
- Awards made to directly support the research.
- No-cost extensions of awards made to support the research.
- "Flow through" federal funds that are awarded to a non-Geisinger affiliated institution and then awarded to Geisinger or affiliate through a subcontract.
- Federal funds that may be indirectly supporting the research such as:
  - Federally funded training grants.
  - Federal scholarships, fellowships, or other training awards such as "K" grants.
  - Federally funded program project grants.
- Involvement of federal personnel.
- Use of federal equipment or materials.
- Use of federal facilities.
- Any research team member (including students) whose time on the research is paid or supported (whether directly or indirectly) by any federal award.

International Research*

*Geisinger international (transnational) research activities are consistent with the ethical principles set forth in its Human Research Protection Program and meet equivalent levels of participant protection as research conducted in the Geisinger principal location while complying with local laws and considering cultural context. (**AAHRPP Standard I-3)**.*

* Currently Geisinger does not conduct international research.

Considerations for Informed Consent

*The IRB has and follows written policies and procedures to evaluate the consent process and to require that the Researcherappropriatelydocumenttheconsentprocess.(**AAHRPPElementII.3.F**)*

Refer to Section 12 – Informed Consent and Assent

1.5 Primary Officials, Administrative Individuals of the HRPP

Officials Responsible for the HRPP

The primary responsibility for the Geisinger HRPP lies with the Institutional Official (IO). The Chief Executive Officer (CEO) of Geisinger delegates this responsibility to the IO. Geisinger's Board of Directors appoints the CEO. The CEO appoints the IO and the IO signs the Federalwide Assurance of Compliance (FWA) on behalf of the institution and is responsible for:

- Creating, establishing, and maintaining policies and procedures for the HRPP and related research policies and procedures on behalf of Geisinger
- Overseeing the protection of human participants, regulatory compliance, and the implementation of the HRPP for Geisinger
- Appointing and overseeing ad hoc or advisory committees as needed
- Ensuring all components of the HRPP effectively communicate
- Overseeing research investigators and staff, and research administration
- Ensuring independence of the IRB, including the authority to act without undue influence
- Requiring periodic reviews of the HRPP
- Ensuring the HRPP is functional, adequately staffed and funded
    - Annual review of the resources allocated to the HRPP
    - Participation in the annual budget preparation for the HRPP and incorporation of the HRPP budget into the Geisinger budget.

The IO delegates day-to-day operational and oversight responsibility to Director of the IRB Operations and HRPP, who is a full-time administrator and reports to the Vice President, Research

Development and Operation of a Learning Health Care System (LHCS)

The model of the learning healthcare system (LHS) was originally developed by the National Academy of Medicine's Roundtable on Evidence Based Medicine in 2007. The key characteristics of the model focus on real-time capture and use of data for clinical care, discovery, and evidence generation; patient–clinician relationships and advanced patient engagement in clinical care and discovery; alignment of incentives with value and improvement; and a leadership-instilled culture of learning and supportive competency development.

Geisinger continues to evolve as an LHS, with a focus on integrating learning initiatives—research, innovation, a quality improvement—into routine processes of caring for patients. Geisinger seeks to embody all the key elements of a LHS, such as its ability to capture, mine, and analyze data through the electronic health record and enterprise-wide clinical data warehouse, and its development of ProvenCare

initiatives in pioneering innovative, evidence-based strategies to improve quality and control costs. The LHS model emphasizes patient-centered, value-based care delivery by utilizing information technology more effectively; creating systems to manage complexity; making health care safer; improving transparency; promoting teamwork and communication; partnering with patients and families; and decreasing waste and increasing efficiency.

To operationalize the LHS at Geisinger, a framework has been developed. The framework consists of nine components representing structures, actions and initiatives needed to achieve progress in implementing the LHS model. The components of the framework include: 1) Data and Analytics; 2) People and Partnerships; 3) Patient and Family Engagement; 4) Ethics and Oversight; 5) Evaluation and Methodology; 6) Funding; 7) Organization; 8) Prioritization; and 9) Deliverables.

The ethics and oversight component addresses the promotion and integration of an ethical framework into all learning activities and the development of an oversight system capable of addressing the changing environment of organizational research and learning.

A structural feature of a learning healthcare system is its intentional blurring of the traditional distinction between biomedical research and clinical care. Initial steps have been taken at Geisinger to think through, as well as act upon the implications of these developments—especially for the work of the Institutional Review Board (IRB) and the Office of Research Compliance (ORC). IRB members have been introduced to issues and challenges situated at the convergence of Common Rule reform and innovation in the ethics of discovery for learning health care systems.

The efforts of Geisinger's research community are supported by an administrative infrastructure, designed to provide operational, financial, managerial, human resources, compliance, and training support to researchers, as well as to comply with the myriad requirements that govern research and the receipt of external grants and contracts. In its mission to "grow, serve, protect and support," Geisinger research facilitates the growth of the research community, provides support to investigators and their staff, interfaces with funding agencies, ensures compliance with federal and institutional requirements, and facilitates interdisciplinary collaboration and external partnerships and support research programs across all departments, centers, institutes, fields and disciplines within the Geisinger system.

IRB Leadership Committee

The IRB Leadership Committee is comprised of the following: Chair, Department of Bioethics and Decision Sciences; Chief Bioethics Officer, Chair, Department of Population Health Sciences. IRB Chair(s); IRB Manager; and Director, IRB Operations and HRPP. Other individuals with IRB leadership experience may be recommended and added at the discretion of the Chair. Chair, Department of Bioethics and Decision Sciences chairs this committee, which serves as an advisory board to the IRB.

Research Ethics Advice and Consulting Service

This free service provides Geisinger investigators, program managers, and other members of the research community with timely consultation on ethical issues in the design and conduct of research (including but not limited to research involving human participants).

Research ethics consultation is a relatively new service increasingly available at major

academic medical centers and other research institutions. It can be valuable in the following scenarios:

- Advice on ethical issues in the design and conduct of research (e.g., recruitment, participant selection and incentives, consent, study design, return of primary or additional results) prior to IRB review (it can save time if ethical issues are identified and a considered plan to address them is proposed prior to IRB protocol submission)
- Advice on ethical issues involving human subjects research that may fall outside the mandate of the IRB (e.g., data sharing, publication ethics, responsible communication of results, concerns about risks of the research to non-participants such as stigmatization, conflicts of interest)
- Advice regarding activities that are not subject to, or are exempt from, IRB or other formal review (e.g., QA/QI; research using decedent data, existing non-identifiable data or specimens, or public data; stem cell research; chimeras)

Unlike IRB and similar compliance reviews, this service is advisory only. Advice given does not in any way substitute for IRB, IACUC, or other required institutional review, nor does complying with said advice guarantee later approval by these committees. Similarly, research ethics advice does not constitute legal advice, even if regulations such as the Common Rule or HIPAA are discussed. Finally, the service is not designed to "pre-review" consent documents or protocols prior to IRB submission; rather, the research ethics consultant works directly and collaboratively with investigators and other personnel who have questions or concerns about consent, protocols, or other aspects of research.

Anyone at Geisinger who is engaged in or considering research or other learning activity may request a consult at any time. In some particularly complex cases, the IRB may request that an investigator obtain a consultation prior to initial IRB review, resubmission, or continuing review. When a project implicates both research and clinical practice, the Research Ethics Advice and Consulting Service may work jointly with the Clinical Ethics Advice and Consulting Service in providing advice. Consultation requests, communication, and meetings are kept confidential to the extent allowable by law.

IRB

The IO officially appoints the IRB Chair(s). The IRB Chair(s), after consultation with the Director IRB Operations, and HRPP appoint the IRB members. The IO assigns the authority and responsibility of the Chair(s) and members to perform, in an independent and autonomous manner, the key functions of the IRB. The IRB is functionally independent (e.g., of the individuals who are conducting the research) and has ready access to the highest officials of the covered organizations, if needed, to ensure protection for human research participants. IRB authority, membership requirements, and responsibilities are described in *Section 6 - Structure and Composition of the IRB*. The IRB is responsible for the initial and continuing review, review of modifications, determining serious or continuing non- compliance, approving, requiring modification(s) (to secure approval), disapproving research, and applying applicable ethical standards.

*Geisinger ensures that the Human Research Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that Geisinger conducts or oversees. (**AAHRPP Standard I-2**)*

Geisinger also participates in the Adult and Pediatric Central Institutional Review Board (CIRB) Initiative of the National Cancer Institute (NCI). The CIRBs are the IRB of record for certain adult and pediatric national multi-center cooperative oncology group cancer treatment trials. Each study is first submitted through Geisinger's electronic database (iRIS) for completion of an administrative review by Geisinger IRB staff to determine if ceding is appropriate. A ceding acknowledgement letter is sent prior to submission of any studies to CIRB.

IRB Staff*:* The Director, IRB Operations and HRPP is responsible for the daily operations of the IRB. IRB staff review study submissions for accuracy and completeness and act as liaisons between Principal Investigators (PI's) and study team and IRB members. Each individual area within the HRPP is responsible for assuring training for all individuals who are affected by the Human Research Protection Program.

Upon request, the IRB has responsibility for review and comment on proposed external regulations dealing with human research. When appropriate, the IRB formulates and recommends draft policies and procedures for approval by the appropriate Geisinger personnel.

Researchers

Program Director/Principal Investigator: The individual responsible for a protocol is the Principal Investigator (PI). Geisinger policy, *Principal Investigator – Program Director Status,* outlines who can serve as a PI. PI responsibilities are specified in *Section 15 – Investigator Requirements* and include ensuring:

- Geisinger human subjects research receives initial prospective review and approval by the IRB.
- Continuing review and approval of the research has been accomplished within the period stipulated by the IRB.
- The research is always conducted in compliance with all applicable regulatory requirements and the determinations of the IRB.

Other Members of the Research Team: Every member of the research team is responsible for protecting human participants. Sub/Co-investigators, study coordinators, nurses, research assistants, and all other research staff have the following strict obligations to:

- Comply with all IRB determinations and procedures
- Adhere rigorously to all protocol requirements
- Inform the PI, and thus IRB, of unanticipated problems and/or possible incidents of non- compliance.
- Ensure the adequacy of the informed consent process
- Take necessary measures to ensure adequate protection for study participants.

Sponsors

Sponsors can be a federal agency, company, institution, individual donor, or organization responsible for the initiation, management, support, or financing of a research study. Both the sponsor and Geisinger have obligations to protect research participants.

Research Participants

Participants in human subjects research also have responsibilities. Responsibilities include telling the truth, asking for clarification, following the protocol, notifying study personnel of his/her non-compliance, and telling investigators if they wish to withdraw from the study.

HRPP Organizational Components

Intellectual Property Management Committee: A committee appointed to receive, review, discuss, and evaluate disclosures of intellectual property made by Geisinger personnel and determine whether there is interest is providing institution support and resources to pursue the protection, development, and commercialization of such intellectual property.

Institutional Conflict of Interest Committee (ICOIC): A committee established by Geisinger to assist with reviewing and managing actual and apparent conflicts of interest that may arise in the normal operations of the various System entities because of individual and institutional relationships with outside organizations. The ICOIC works in collaboration with the appropriate departments, employees, officers, and other committees to control and manage related conflicts of interest.

Research Conflict of Interest Committee (RCOIC): Research Conflict of Interest Committee (RCOIC): Geisinger has established a system-wide Research Conflict of Interest Committee (RCOI Committee), which is responsible for establishing and communicating standards with respect to research related Conflicts of Interest and carrying out the review and disposition of such potential Conflicts of Interest. The RCOI Committee is responsible for control and management of all research related Conflicts of Interest, including development and oversight of a management plan to eliminate, reduce or manage actual or apparent Conflicts of Interest. The RCOI Committee will document its findings and the basis for its decision with respect to any research; such documentation will be made available to the appropriate research regulatory committee, e.g., IRB. To the extent possible and as allowed by law, all Conflict-of-Interest Questionnaires and related information shall be kept confidential and may only be shared with other individuals identified case by-case on a need-to-know basis (e.g., Institutional COI Committee, IRB). Director, IRB Operations and HRPP, is a member of the RCOIC.
See *Geisinger Policy on Financial Conflicts of Interest in Research* for reporting details and policy. Section 3.7 also provides additional details.

I***nstitutional Biosafety Committee (IBC)***: The IBC establishes and implements policies that provide safe conduct of research involving biohazards and ensures compliance with the NIH Guidelines for Research Involving Recombinant DNA Molecules. Biohazards are defined as biological agents that are potentially hazardous to humans or animals. This includes known pathogens and infectious agents including bacteria, their plasmids, and viruses. The IBC is comprised of a minimum of five members selected so that collectively they have experience and expertise to provide guidance on projects that include, but are not limited to, recombinant DNA, RNAi, pathogens, human materials, and other potentially infectious material, as well as transgenic animals. The committee's responsibility is to assess the safety of proposed research and to identify risk to the public health or environment. All human research studies involving recombinant DNA molecules or handling of biohazardous materials must be submitted and approved by the IBC prior to submission and review of the study by the IRB. The IBC approval letter is submitted to the IRB.

Radiation Safety Committee (RSC): The Radiation Safety Committee has institutional responsibility for oversight of the use of radioisotopes and lasers and works closely with Medical Health Physics to implement policies and procedures related to safety. Prior to IRB submission, any research study involving human subjects that will use ionizing radiation must be reviewed and approved by the RSC if the use of radiation goes beyond that established for the applicable standard of care. The RSC approval letter is submitted to the IRB.

Corporate Compliance Program: Various departments and committees enforce the Corporate Compliance Program throughout with oversight residing under the Geisinger Board of Directors.

Information Security Office (ISO): The Information Security Office cultivates an environment that protects and preserves the confidentiality, availability, and integrity of Geisinger, its entities, patient's data, and resources. ISO's mission supports the organizational mission of enhancing quality of life through an integrated health service organization based on a balanced program of patient care, education, research, and community service. Geisinger ISO, in collaboration with Privacy Office and IT Compliance, perform Security, Compliance, Privacy (SCP) risk assessments for transmission of patient data for research purposes. Any human research study that includes transmission of identifiable data must be submitted and reviewed via the SCP process prior to protocol submission to the IRB. The SCP assessment and review outcome is submitted to the IRB.

Privacy Office: The Privacy Office is committed to protecting the privacy and confidentiality of its patients' and members' medical information in compliance with state and federal law. To help create a culture of trust, the Privacy Office:

- Protects and enforces patient's rights
- Provides education, awareness, and training
- Investigates complaints
- Responds to and remediates impermissible uses and disclosures
- Conducts risk assessments and monitors privacy compliance

Department of Legal Services: The Department of Legal Services is responsible for addressing the legal issues arising out of the activities of Geisinger and is available for consultation on issues regarding human subjects' research, participant protections and compliance with applicable local, state, and federal law.

Scientific Review Committee (SRC): The SRC provides peer review of investigator-initiated research that is greater than minimal risk studies if the study was not subject to external scientific review. The SRC also assesses scientific merit of study submissions requesting funds from the Geisinger Research Board Designated Endowment Fund. The research team receives an SRC letter documenting that the protocol was found to be meritorious. This letter must be submitted to the IRB.

MyCode® Governing Board: MyCode® Community Health Initiative is the Geisinger Biobank, a key research resource. The MyCode® Governing Board provides strategic guidance to the Geisinger MyCode® project and is the primary steward of MyCode resources. The My Code® Governing Board reviews all requests for MyCode banked samples and related DNA sequencing results. The MyCode Governing Board approval letter must be submitted to the IRB.

Office of Sponsored Projects: The Office of Sponsored Projects (OSP) provides a central point for the review and approval of research and other sponsored projects being submitted by Geisinger personnel

for externally sponsored projects, projects funded by the Clinic Research Fund, and/or all proposals with patient care or billable patient events. Because these proposals commit Geisinger resources (people, facilities, equipment, and other assets), it is necessary they be reviewed to ensure they meet Geisinger policies and are consistent with Geisinger's
mission. Additionally, proposals are reviewed for adherence to federal laws governing research and the sponsor's policies for the preparation and submission of grants and contracts and clinical trials. OSP negotiates awards, issues subawards or contracts, helps prepare budgets, reviews terms and conditions, and provides general advice related to sponsored projects. All research studies that include patient care charges are required to submit a Billing Determination (BD) to OSP. OSP completes a Medicare Coverage Analysis (MCA) and approves the BD which delineates research versus standard of care charges. A copy of the signed BD needs to be uploaded with the study submission to the IRB to enable thorough IRB review of the consent document. In addition, OSP handles post-award subcontract monitoring, agreements, amendments and invoice review/payments.

Research Finance: Research Finance is responsible for research project accounting and has a role in post-award administration of externally funded research projects and programs at Geisinger. Research Finance reports directly to Geisinger Vice President, Chief Accounting Officer. Research Finance establishes new project activities, invoices sponsors, prepares financial reports required by the sponsors, produces monthly Budget versus Actual (BVA's) and cash reports as well as patient care reports, and closes expired sponsored projects. Research Finance also provides guidance on post-award research administrative topics including the allowability of costs on sponsored projects, effort certification, cost share, program income and other compliance related topics.

Nursing Research Council (NRC): The mission of the NRC is to facilitate quality improvement, evidence-based nursing practice and nurse-initiated research. IRB study applications capture whether nursing staff are involved in the project. If so, the NRC tracking number is captured in the study application indicating NRC review of the scholarly activity.

Investigational Drug Service Pharmacy (IDS): The IDS Pharmacy provides services for clinical trials throughout Geisinger. The IDS Pharmacy is charged with the safe and responsible handling of investigational drugs. By maintaining control and accountability of investigational drugs used within the system, subject safety is maximized. All research studies involving investigational drugs must be submitted to the IDS pharmacy for review. The IDS Authorization Number is captured in the IRB Study Application.

Marketing & Communications: Marketing & Communications plays a crucial role in communicating the mission, vision, and values of Geisinger to physicians, professional staff, volunteers, patients, and the community at large. Marketing & Communications offers public relations, marketing, digital, graphic design, and employee communication strategies for Geisinger. Geisinger-developed research posters or recruitment advertisements and digital recruitment messaging must be reviewed by Marketing & Communications. Confirmation of the review must be submitted to the IRB.

1.6 Ethical and Legal Principles Governing Human Subjects Research

Ethical Principles

The primary ethical principles applied to research covered by the HRPP, including protocols "exempt"

under federal regulations pertaining to human subjects research, are those set forth in the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*.

The three main principles are:

1. ***Respect for persons*** (e.g., applied by obtaining informed consent, considering privacy and confidentiality, and adding protections for vulnerable populations)
2. ***Beneficence*** (e.g., applied by weighing risks and benefits)
3. ***Justice*** (e.g., applied by the equitable selection of subjects)

All research staff involved in the conduct of research are expected to also adhere to the principles of expertise ("competent to do the work") and integrity ("faithfully adhere to professional principles"). Ethical principles from other sources (e.g., International Conference on Harmonization) may also be applied to research covered by the HRPP, for example:

- To an individual protocol because its circumstances raise a type of ethical issue that most other protocols do not
- When they are recognized by the federal or other funding source or the state where the research will occur
- When they have been developed for specific areas or types of subjects (e.g., embryos and fetal tissue, illiterate subjects).

Investigator training regarding ethical principles governing human subjects research and investigator responsibilities is covered in the CITI training module for investigators, IRB Members, and IRB Staff.

With respect to sponsored research, Office of Sponsored Projects (OSP) addresses the protection of research participants by including a provision that the sponsor acknowledges and understands that the Geisinger HRPP is applicable to all human participant research in Geisinger standard contract templates. (See *Section 16 - HRPP Coverage of Sponsored Research*)

Legal Principles

The basic legal principles governing human subjects research, covered by the HRPP and applicable to individual protocols, are:

- 2018 Revised Common Rule - 45 CFR 46
- Food and Drug Administration Regulations - 21 CFR 11, 50, 56, 312, and 812
- Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) - 45 CFR 160 and 164
- Applicable state law

These and other legal principles are addressed when applicable in individual sections of the HRPP Handbook.

*Geisinger has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board or Ethics Committee, as appropriate. (**AAHRPP Element I.1.D**)*

1.7 Scientific and Scholarly Validity Review and Ethics Review

*Geisinger has and follows written policies and procedures for reviewing the scientific or scholarly validity of a proposed research study. Such procedures are coordinated with the ethics review process. (**AAHRPP Element I.1.F**)*

Scientific and Scholarly Validity Review

When evaluating the scientific and scholarly validity of a protocol, the IRB relies on the review provided by different entities, as follows:

- For federally sponsored research, the peer review process by the sponsoring agency (e.g., NIH, NCI,) provides scientific and scholarly review.
- For research subject to FDA review, the FDA conducts a rigorous scientific design review during IND or IDE evaluation. Most industry-sponsored research falls within this category. An important exception is Non-Significant Risk (NSR) device research, where the IRB serves, in a sense, as the FDA's surrogate with respect to review and approval of NSR studies.
- Geisinger Scientific Review Committee (SRC) provides peer review of investigator-initiated research that is greater than minimal risk studies if the study was not subject to external scientific review. The SRC also assesses scientific merit of study submissions requesting funds from the Geisinger Research Board Designated Endowment Fund. The research team receives an SRC letter documenting that the protocol was found to be meritorious. A copy of the letter must be uploaded with the study submission to the IRB.

*Geisinger ensures that the Human Research Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that Geisinger conducts or oversees. (**AAHRPP Standard I-2**)*

For ***all*** research, the IRB evaluates, in accordance with applicable federal research regulations [45 CFR 46.111(a) and 21 CFR 56.111(a)], whether the following requirements are satisfied:

1. Risks to participants (physical, psychological, social, legal, and economic) are minimized(i) by using procedures that are consistent with sound research design and that do not unnecessarily expose participants to risk; and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
2. Risks to participants are reasonable in relation to anticipated benefits, if any, to participants, and the importance of the knowledge that may be expected to result.

If the requirements noted above are not satisfied, the protocol may not be approved as written. The IRB reviewer(s) may consider other scientific reviews, as noted above, (e.g., NIH peer review, SRC review) in the evaluation. For protocols where the protocol design is unusual or novel, in addition to the protocol being assigned to primary reviewer(s) with relevant expertise, input from ad hoc consultants may also be obtained. For further information, refer to Guidance Evaluating Sound Study Design.

Ethics Review

IRB review of the study procedures, risks and benefits includes the identification, evaluation and resolution of ethics issues presented in the study in accordance with the ethical principles outlined in *Section 1.6-Ethical and Legal Principles Governing Human Subjects Research*. The IRB may seek ad hoc assistance from Geisinger Chief Bioethics Officer and Chair, Department of Bioethics and Decision Sciences, who service as ex officio members of the IRB. In addition, Researchers and the IRB can request assistance from Geisinger's Research Ethics Advice Consulting Service.

Section 2 - Resources Supporting the HRPP

2.1 Sufficient Human and Fiscal Resources

*Geisinger ensures that the Human Research Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that Geisinger conducts or oversees. (**AAHRPP Standard 1-2**)*

The provision of adequate human and financial/fiscal resources is facilitated through Geisinger's annual budgeting process and regular meetings between Geisinger IRB leadership and Research Leadership, which results in a well-functioning and effective HRPP.

Human Resources: Geisinger demonstrates a high level of institutional commitment to its HRPP in terms of human resources. The HRPP is led by the Institutional Official (IO), pursuant to the authority delegated by the Chief Executive Officer (CEO) (see Delegation of Authority to Institutional Official). The IO oversees the Institutional Review Board (IRB) Operations and HRPP.

Financial Resources: Geisinger demonstrates a high level of institutional commitment to its HRPP in terms of financial resources and is committed to providing the IRB with adequate means to carry out its mission while maintaining protocols-to-staff-ratio within acceptable and manageable limits.

Resource Allocation in support of HRPP: Adequate human and financial/fiscal resources for HRPP are provided by Research leadership. HRPP is part of Geisinger's central research administrative structure, operationally reporting to Geisinger VP, Research. Operational costs of the HRPP are considered indirect costs and as such are covered in the federal indirect cost rate calculation. IRB fees are charged directly to research studies externally sponsored by not-for profit entities based on a published fee schedule to assist with offsetting the cost of HRPP. In addition, single IRB fees are charged for review of non-Geisinger entities participating in cooperative research for which Geisinger IRB is serving as the single IRB.

2.2 Review of IRB Activity, Including Volume and Types of Human Research

*Geisinger ensures that the Human Research Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that Geisinger conducts or oversees. (**AAHRPP Standard 1-2**)*

The IRB regularly assesses activity to optimize workflows, IRB load and staffing needs. It considers the ratio of protocols to staff, the number of transactions generated by each protocol, the type of protocols (regular, expedited or exempt), and any other appropriate elements. Input from the IRB staff and Chair(s) regarding the level of activity and other IRB-related matters are presented at monthly meetings with VP, Research, and quarterly meetings with Research leadership, including the IO. When adjustments are necessary, their financial implications are considered during the annual budget process. New staff positions are created to meet the demands of the workload.

2.3 iRIS by iMedRIS

Geisinger's IRB utilizes an electronic submission platform, iRIS. iRIS integrates Institutional Review Board (IRB) management and data collection into a web-based application.

iRIS allows the following:

- Electronic study submissions by Research staff
- Electronic review by IRB members and staff
- Electronic checklists and reviewer sheets used by IRB members and staff
- Electronic correspondence records between IRB and research staff
- Electronic creation and modification of IRB review documentation
- Electronic approval of study documents, including consent or HIPAA forms and protocols
- Electronic documentation of IRB meeting attendance
- Electronic documentation of IRB meeting votes
- Electronic access to "live" study submission material by study team and IRB members
- Electronic documentation and merging of IRB member comments, recommendations, and stipulations into minutes.

2.4 Human Research Protection, Care of Participants, and Safety

*Geisinger ensures that the Human Research Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that Geisinger conducts or oversees. (**AAHRPP Standard I-2**)*

To approve research, the IRB must determine that, where appropriate, there are adequate resources to ensure the care and safety of participants throughout the project, beginning with the screening and recruitment phases. During review of the submitted protocol, the IRB members have access to all information in the iRIS Study Submission packet (application, protocol, consent form, etc.) and as necessary may ask for additional details. (See *Section 7- Systematic Review for information about the review process*) If the protocol does not provide adequate protection, the study cannot be approved.

Principal Investigators (PIs) are required to indicate in the study submission whether investigators will have: access to a population that will allow recruitment of the required number of participants; sufficient time to conduct and complete the research; adequate numbers of qualified staff; adequate facilities; a process to ensure that all persons assisting with the research are adequately informed about the protocol and research related duties and functions; and medical or psychological resources available that participants might require as a consequence of the research when applicable. This attestation is included in the electronic PI sign-off in the iRIS study submission.

When the protocol has billable events or patient care charges and the protocol is not funded by a contract or a grant, the availability of resources is affirmed by the department head signing the OSP Transmittal Form. PIs should continually monitor the resources allocated for the research and notify the IRB if any change in the availability of resources may adversely impact the rights and welfare of participants.

2.5 Communication and Interaction

*Geisinger has and follows written policies and procedures setting forth the ethical standards and practices of the human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board, as appropriate. (**AAHRPP Element I.1.D**)*

Communication and Interaction

The IRB requires that appropriate communications from the following offices or committees are complete. The IRB works closely and communicates often with the following committees and departments to discuss study-specific topics and develop processes to enhance communications and workflows essential to facilitating effective and efficient review of human subjects' research. Study submissions are reviewed to ensure that situations requiring communication and interaction between various components of the HRPP are handled appropriately:

- **Radiation Safety Committee (RSC)** - The study team submits the protocol to the RSC for review. The RSC certifies it has reviewed a protocol using ionizing radiation, recommends it for approval, and provides informed consent risk language. A copy of the RSC approval must be uploaded with the submission to the IRB.
- **Institutional Biosafety Committee (IBC) –** The study team submits the protocol involving recombinant DNA molecules or handling of biohazardous materials to the IBC for review prior to submission and review of the study by the IRB. A copy of the IBC approval letter is uploaded with the study submission to the IRB. If an amendment/modification or continuing review involves review by the IBC, the IRB will approve until IBC approval is submitted to the IRB.
- **Office of Research Compliance (ORC)** reviews all Investigator Conflict of Interest disclosures. Investigator conflict of interest is managed by ORC staff via COI Smart with involvement of the Research Conflict of Interest Committee (RCOIC) as necessary. COI Smart is web-based platform that provides comprehensive tools for tracking and managing Conflict of Interest (COI) disclosures. COI Smart provides for the development of multi-level branching questionnaires, automated assignment of reviewers, development of COI management plans, and tools for auditing, tracking, and reporting on potential conflicts of interest. When potential COI is identified, ORC works closely with Geisinger RCOIC to determine whether the potential conflict can be managed or needs to be eliminated and approves management plans when developed to mitigate the potential conflict. The IRB will not approve a protocol until any disclosed COI has been reviewed by the Research Conflict of Interest Committee, and as appropriate, a plan or strategy to eliminate, mitigate, or manage the conflict has been determined. All management plans are submitted to the IRB for review and approval. See *Sections 3.7 - Conflicts of Interest (COI)* and *6.6 - IRB Member, IRB Staff, and Consultant Conflicting Interest*.
  ORC is responsible to administer Geisinger's research training requirements and relationship with CITI, where Geisinger-required research modules are located. CITI interfaces with iRIS and uploads a daily report of all completed CITI training for Geisinger-affiliated users. ORC staff review CITI "expired training" reports monthly and coordinate a process to ensure study personnel complete training or are removed

from studies. When not successful, ORC elevates the issue to designated IRB staff, who works with study PIs to resolve the issue.
ORC staff work with ORC staff to conduct secondary review and approval of all Medicare Coverage Analyses (MCA) and Billing Determinations (BD) for all research that will incur billable charges. These approved documents must be submitted to the IRB.

- **Office of Sponsored Projects (OSP)** – OSP coordinates sponsored contracts, grant funding, and Material Transfer Agreements (MTAs) for transfer of blood, tissue, or data (slides, X-rays, etc.) in or out of Geisinger when there is no contract in place. All data sharing agreements (e.g., agreement for disclosure of PHI and data use agreements) are facilitated by OSP staff. For studies where the IRB has granted waiver of consent/authorization and disclosing PHI outside Geisinger one of the following must be done: data sharing details included in the clinical trial agreement, contract, sub-award, or data sharing agreements must be finalized prior to release of data.
  All research studies that include patient care charges are required to submit a billing determination (BD) to OSP. OSP completes a Medicare Coverage Analysis (MCA) and approves the BD which delineates research versus standard of care charges. A copy of the signed BD needs to be submitted to the IRB to enable thorough IRB review of the consent document.
  In addition, IRB approval for externally sponsored research includes final OSP review to conduct reconciliation of the protocol, informed consent, billing determination, budget, and contract/clinical trial agreement/award. Documentation of reconciliation is submitted to the IRB to transition the review outcome from "pending IRB approval" to "IRB approval."
- **Investigational Drug Service (IDS) -** Any protocol involving the administration of an investigational drug or investigational new drug (oversight by the FDA) to human research subjects must have, as a condition of approval, an IDS Authorization Number from the IDS Pharmacy. The study submission must include the IDS Authorization Number to identify that the IDS Pharmacy was contacted and provided input on the appropriate storage, oversight, and dispensing of the investigational drugs or biologics. (See *Section 5.2- Research with Test Articles*)
- **Nursing Research Council (NRC) -** the NRC facilitates quality improvement, evidence-based nursing practice and nurse-initiated research. IRB study applications capture whether nursing staff are involved in the project. If so, the NRC tracking number is captured in the study application indicating NRC review of the scholarly activity.
- **Geisinger Commonwealth School of Medicine Office of Research Compliance (GCSOM ORC) -** GCSOM ORC assists with facilitation of research and compliance with Geisinger HRPP policies and procedures. GCSOM ORC reviews all research proposals including GCSOM faculty and students prior to submitting to Geisinger IRB for review. GSCOM ORC assigns each submission a tracking number, which is captured in the IRB study application.
- **Scientific Review Committee (SRC) -** Any protocol considered greater than minimal risk requires scientific review. Many protocols are reviewed through peer review at the FDA, a cooperative group, NIH study section or a grant review process. If not, the study must be reviewed by the SRC prior to submission and review by the IRB. The research team receives an SRC letter documenting that the protocol was found to be meritorious. A copy of the letter must be uploaded with the study submission to the IRB.
- **Marketing & Communications -** Marketing & Communications plays a crucial role in communicating the mission, vision, and values of Geisinger to physicians, professional staff, volunteers, patients, and the community at large. Marketing & Communications offers public

relations, marketing, digital, graphic design, and employee communication strategies for Geisinger. Marketing & Communications must review Geisinger-developed research posters or recruitment advertisements and digital recruitment messaging. Confirmation of the review must be submitted to the IRB.

- **Security, Compliance, Privacy (SCP) Review -** Geisinger Information Security Office (ISO), Privacy Office and IT Compliance perform Security, Compliance, Privacy (SCP) risk assessments for all studies that transmit patient data for research purposes outside of Geisinger covered entities. Any human research study that includes transmission of identifiable data must be submitted and reviewed via the SCP process prior to protocol submission to the IRB. A copy of the SCP assessment is uploaded with the study submission to the IRB.

Policies

The HRPP Handbook and other relevant policies and procedures are available to the entire Geisinger research community, including researchers, research staff, IRB staff, IRB members, employees, students, and the public through Geisinger's Human Research Protection Program internal and external websites, and various other sources as described in *Section 3.1- Policies, Procedures, and Resources Available to Investigators and Research Staff*.

Section 3 - Compliance Monitoring

3.1 Policies, Procedures, and Resources Available to Investigators and Research Staff

*Geisinger has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board, as appropriate. (**AAHRPP ElementI.1.D**)*

The Office of the Institutional Review Board (IRB) has primary responsibility for ensuring the HRPP Handbook, Guidance documents and related relevant materials are available to the Geisinger research community, including:

- Investigators
- Research staff
- IRB staff
- IRB members
- Faculty
- Employees
- Students
- Participants

Relevant policies and procedures are available internally on Geisinger HRPP SharePoint and externally on Geisinger.org. Examples of available resources located on the HRPP sites include:

- HRPP Handbook
- Links to pertinent governmental regulations and guidelines
- Links to relevant Geisinger policies
- Guidance on various topics, such as sponsor-investigator research, children in research, use of test articles and reportable events
- Checklists and templates for protocol, consent/assent form, and HIPAA authorization development
- iRIS overview and instructions
- Guidance for investigators regarding human subjects' research protections and the IRB review process
- Research Determination Worksheet (RDW) submission process
- Alerts highlighting the posting of new information or changes in existing policies and procedures
- Educational presentations

The IRB utilizes the following mechanisms to provide education, information, and guidance to the Geisinger research community related to human research protections, regulations, IRB policies and procedures governing human subjects research, as well as communicate changes in policies, procedures, and guidance:

- HRPP website updates
- Important iRIS Announcements – notifications via "blast" email communications from iRIS to all active

users, including Administrators, Investigators, Research Staff, IRB Members and Staff, Office of Sponsored projects, Research Finance, and Office of Research Compliance

- Digital communications to Geisinger research community via:
  - Geisinger Research Teams Channel
  - Geisinger "Research Community" email group
- Presentations to the Research community at venues, such as:
  - Geisinger Research Faculty & Staff Meeting (quarterly)
  - Geisinger Research Faculty Meeting (monthly)
  - Geisinger Clinical Research Grand Rounds (monthly)
  - Responsible Conduct of Research Didactic Training (quarterly)
  - Research and clinical department meetings
- IRB Member Education:
  - New member orientation
  - New member Mentor-Mentee Program
  - IRB member training sessions (typically held quarterly and ad hoc)
  - Archived training sessions
  - Individual member meetings with IRB staff

The IRB staff is readily available to assist investigators and research staff on all human subjects' research matters.

3.2 Independence of IRBs

*Geisinger has and follows written policies and procedures that allow the Institutional Review Board to function independently of other organizational entities in protecting research participants. (**AAHRPP Element I.1.C**)*

Organizational Structure that Provides Independence

The Chief Executive Officer (CEO) of Geisinger has delegated the authority and responsibility to establish, maintain and oversee the HRPP to the Institutional Official (IO) as specified in the Delegation of Authority letter.

The IO officially appoints the IRB Chair(s). The IRB Chair(s), in consultation with Director, IRB Operations and HRPP, appoint the IRB members. The IO assigns the authority and responsibility of the Chair(s) and members to perform, in an independent and autonomous manner, the key functions of the IRB. The IRB is functionally independent (e.g., of individuals who are conducting the research) and has ready access to the highest officials of the organization, if needed, to ensure protection of human research participants.

IRB authority, membership requirements, and responsibilities are described in *Section 6 - Structure and Composition of the IRB*.

Delegation to the IRB

The IO delegates independence and authority to the IRB through the *Charge to IRB Members by*

Geisinger's Institutional Official. The IRB has the authority to:

- Review, approve, disapprove, or require changes in research involving human participants.
- Suspend or terminate research involving human participants or an investigator's privilege to conduct such research (e.g., in situations where research is not being conducted in accordance with IRB requirements, or where the research has been associated with unexpected serious harm to participants).
- Observe, or have a third party observe the consent process; and
- Observe, or have a third party observe the conduct of research.

Prohibition against Others Usurping IRB Approval Authority or Using Undue Influence

The IO prohibits Geisinger officials, investigators, and employees, and sponsors contracting with Geisinger for research from:

- Maintaining or claiming IRB approval of research that has been disapproved or not yet been reviewed by the IRB
- Attempting to use or using undue influence with the IRB, any of its members or staff, a PI, or any other member of the research team to obtain a particular result, decision, or action.

"Undue influence" means attempting to interfere with the normal functioning and decision- making of the IRB or to influence an IRB member or staff, a PI or any other member of the research team outside of 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.

An individual who believes he or she has been subjected to such undue influence should report it to the Director, IRB Operations and HRPP. Reports of attempts to unduly influence individuals involved in human subjects' research operations or review of such research will be reviewed and addressed by the Director in consultation with Geisinger IRB Chair(s) and IO.

The IRB preserves the anonymity of members assigned as reviewers to specific protocols or protocol events and members of the study team do not have access to the reviewer's comments. The IRB staff communicate all comments from the reviewer to the research team via official correspondence unless the reviewer permits direct access.

3.3 Regulatory Definition of Human Subject Research

*Geisinger has and follows written policies and procedures for determining when activities are overseen by the Human Research Protection Program. (**AAHRPPElementI.1.A**)*

"Research" and "human subject" are defined in the 2018 Common Rule (45 CFR 46.102) and "clinical investigation" and "human subject" are defined in FDA regulations (21 CFR 50.3).
At Geisinger, IRB retains authority to determine whether an activity meets the definition of "human subjects research." IRB staff will make a timely determination after receipt and review of a completed Research Determination Worksheet Study Application. Outcome of the IRB staff review is communicated to the PI via an IRB outcome letter. The outcome letter provides documentation of the determination about whether the activity meets the definition of human subject research as defined in 45 CFR 46.102.

Section 1.4 - Research Covered by the HRPP describes the types of human subjects' research conducted at Geisinger.

All "research" involving "human subjects" must be reviewed and approved by the IRB **before** research activity can begin.

3.4 Exempt Research Determinations

*The IRB has and follows written policies and procedures for determining when activities are exempt from applicable laws and regulations, when permitted by law or regulation and exercised by the IRB. Such policies and procedures indicate that exemption determinations are not to be made by Researchers or others who might have a conflict of interest regarding the studies. (**AAHRPP Element II.2.A**)*

Categories of exempt research are stipulated in, and exempt determinations are based upon the following federal regulations and Geisinger HRPP Guidance.

- **Federally sponsored research** - 2018 Common Rule (45 CFR 46.104). Please note: Geisinger IRB does not consider exempt determinations based on 2018 requirements for Exemption categories 7 and 8.
- **FDA-regulated research** - 21 CFR 56.104, which includes *Emergency use of a test article*. (*See Section 5.6 - Other Access to Investigational Drugs and/or Devices)*

Exempt status shall not be granted when

Research involves prisoners as participants, except for research aimed at involving a broader subject population that only incidentally includes prisoners

Research is subject to FDA regulations except as permitted in 21 CFR 56.104

If there are interactions with participants, they should be provided with information about the research and an opportunity to prospectively agree to participation in the research.

Making Exemption Determinations without Conflict of Interest

IRB members and staff involved in reviewing and approving the exempt determination of study submissions must not participate in the review of protocols in which they have a conflicting interest. *Section 6.6- IRB Member, IRB Staff, and Consultant Conflicting Interest* describes policies prohibiting such situations.

3.5 Policies and Procedures for Exempt Research

*The IRB has and follows written policies and procedures for addressing protection of participants in research that is exempt from applicable laws and regulations. These functions may be delegated to an entity other than the IRB. (**AAHRPP Element II.2.B**)*

Geisinger requires protocols potentially qualifying for designation as exempt to be submitted for IRB review and confirmation of exempt status. While such research is exempt from the regulations set forth in 45 CFR 46.104, and 21 CFR 56.104 (FDA), the research must meet Geisinger HRPP ethical standards governing the conduct of research. *(See Section 1.6 - Ethical and Legal Principles Governing Human Subjects Research.)* Please note: Geisinger does not make exempt determinations based on 2018 Common Rule Exemption categories 7 and 8:

The IRB requires exempt protocols provide appropriate protections for privacy of research participants and confidentiality data. *(See Section 11- Privacy and Confidentiality)*

Exempt Review Process

Investigators must submit iRIS Exempt Study Application to Geisinger IRB for review and exempt determination. Review is performed by IRB staff or IRB members who have the knowledge and authority to confirm exemption or refer the protocol for expedited or convened review. Reviewers refer to *Geisinger Exempt Study Application, IRB Reviewer Form* and *Guidance - Exempt Review Categories* to verify the proposed research meets criteria for exemption and the PI has requested an appropriate exemption under the appropriate category.

Please note: New and ongoing minimal risk non-federally sponsored or FDA-regulated studies were evaluated for transition to Exempt status at the time of the study's continuing review occurring on or after May 1, 2018, based on investigator responses to questions related to type of study funding, sponsor or regulated status, participant interaction and research activities. Effective January 21, 2019, HHS Final Rule Exemption categories are applied to all research that is not FDA-regulated.

Several Exemption Categories require "Limited Review" by an IRB member to ensure provisions are adequate to protect the privacy or research participants and confidentiality of data (*effective May 1, 2018, for research not federally supported; effective January 21, 2019, for all federally supported research*).

- **Exemption Category (2)(iii)** – 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) AND 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 that provisions are adequate to protect the privacy or research participants and confidentiality of data
- **Exemption Category (3)(i)(C)** – 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 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 that provisions are adequate to protect the privacy or research participants and confidentiality of data

If a protocol meets the criteria for exemption, an outcome letter is generated and sent to the PI and designated study contact(s).

If a protocol does not meet criteria for exemption, an IRB outcome letter will be sent to the PI and study contact requesting modifications or instructions to submit Revised Common Rule Study Application, which Geisinger IRB requires for protocols reviewed via expedite or convened review processes. The letter will include details specifying why the submission failed to meet the exemption criteria.

Once a protocol is determined to be exempt, ongoing IRB review is not required unless the following revisions are proposed. Amendments are required for the following changes after an Exemption determination:

- Any Proposed Change to Research that Might Impact Exemption Status – You must submit an Amendment/Modification form explaining any change to your research that might affect the exemption determination and might result in changing your research's eligibility for exemption status.
- Key Study Personnel (KSP) – All personnel changes, including both the addition of new personnel and removal of personnel no longer involved in the research that occur after the IRB has granted an Exempt determination must be submitted to the IRB. The KSP Amendment must be submitted and approved before any new personnel begin working on the study. Investigators must submit a KSP Amendment form and revised Exempt Study Application. This requirement is in place to facilitate compliance with and administration of *Geisinger Policy - Financial Conflicts of Interest in Research* and *Geisinger Policy - Research Education and Training*.
- Sponsor/Funding Source – Investigators must submit any change in the study's sponsor/funding source to the IRB since this could impact the IRB's review process and/or determination. Investigators submit an Amendment/Modification form and revised Exempt Study Application. This requirement is in place to ensure review under the correct regulations.
- Data Collection Date Range (Category 4(iii) or "HIPAA Exemption") – Investigators must submit an amendment if the date range for data collection is revised to extend beyond the initial IRB submission date. This requirement is in place because HIPAA regulations apply to this research, and this change in research might impact justification of HIPAA waiver and/or require HIPAA Authorization from participants.

3.6 Federal versus State Requirements

*Geisinger has and follows written policies and procedures that identify applicable laws in the localities where it conducts human research, takes them into account in the review and conduct of research, and resolves differences between federal or national law and local laws. (**AAHRPP Element I.1.G**)*

Geisinger IRB requires investigators comply with the local, federal, and state laws that are applicable to the research. The IRB staff, in consultation with appropriate legal counsel, as necessary, provide advice and education to investigators, research staff, and the IRB about such laws, and assist in resolving any conflicts among applicable laws. If there is conflict, the IRB follows the most stringent of the regulations to assure adequate compliance and human subject protection.

Geisinger has developed guidance for research use and disclosure of highly protected health information (HPHI) to ensure compliance with more restrictive Pennsylvania state laws and federal regulations which govern the use of the following patient records. (Please refer to *HRPP Handbook Section 11.4, Highly Protected Health Information* for additional information.):

- Mental health records subject to *The Pennsylvania Mental Health Procedures Act [50 P.S. § 7103* and *55 Pa. Code § 5100.36(c)]*
- HIV-related information subject to Pennsylvania's *Confidentiality of HIV-Related information Act (35 PS 7601 et seq.)*
- Substance use disorder records subject to *Pennsylvania Drug and Alcohol Abuse Control Act – Confidentiality of Records (71 PS 1690 et seq.)*
- Federally-supported Medication Assisted Treatment (MAT) program substance use disorder treatment records subject to Federal Law – *Confidentiality of Substance Use Disorder Patient Records* (42 CFR Part 2)

Laws of Other States (Research Outside of Pennsylvania)

Investigators may conduct research in states other than Pennsylvania. As each state has different laws, Investigators must adhere to the laws of the state in which research is being conducted.
When necessary, IRB staff consult with appropriate legal counsel and coordinate discussions to provide guidance and interpretation of Pennsylvania and other states' laws.

3.7 Conflicts of Interest (COI)

*Geisinger has and follows written policies and procedures to identify, manage, and minimize or eliminate financial conflicts of interest of the Organization that could influence the conduct of the research or the integrity of the Human Research Protection Program. (**AAHRPP Element I.6.A.**)*

*Geisinger has and follows written policies and procedures to identify, manage, and minimize or eliminate individual financial conflicts of interest of Researchers and Research Staff that could influence the conduct of the research or the integrity of the Human Research Protection Program. Geisinger Conflict of Interest Committee works with the Institutional Review Board in ensuring that financial conflicts of interest are managed and minimized or eliminated, when appropriate. (**AAHRPP Element I.6.B.**)*

*Researchers and Research Staff identify and disclose financial interests according to organizational policies and regulatory requirements and, with Geisinger, manage, minimize, or eliminate financial conflicts of interest. (**AAHRPPElementIII.1.B**)*

Geisinger recognizes the importance of relationships with outside organizations and seeks to encourage such relationships. These relationships can give rise to significant discoveries and to the translation of

those discoveries into useful products. Productive relationships with outside organizations also inspire new avenues of inquiry and provide opportunities to conduct research. However, the financial incentives that accompany such relationships may lead to financial conflicts of interest. Such conflicts of interest have the potential to create real or apparent bias in research. Conflicts of interest may affect research integrity and may place human Research subjects at additional risk. Conflicts of interest, and even the appearance of conflict of interest, may reduce public confidence in the research enterprise. Thus, Geisinger has policies and procedures for identifying financial interests, assessing and mitigating related potential conflicts of interest arising from such interests.

Policies for Research

Geisinger Policy on Financial Conflicts of Interest in Research, which complies with Conflict of Interest regulations of the U.S. Public Health Service (42 C.F.R. Part 50, Subpart F and 45 C.F.R. Part 94), applies to all Investigators conducting research at Geisinger, whether or not federally funded, and research regulatory committee members (e.g., IRB, RSC, IBC). This policy dictates requirements and processes for education, disclosure, review, and outcomes of potential conflicts of interest related to research (e.g., COI management plan development and approvals).

Geisinger, as an organization, may enter into relationships that might create potential conflicts of interest. A duality or even multiplicity of interests can be beneficial to, and consistent with, the primary goals of the organization, but they can also raise the potential for a conflict of interest related to research conducted at Geisinger. Geisinger addresses such potential conflicts on a case-by-case basis.

Geisinger Office of Research Compliance (ORC) staff have established processes to facilitate identification, review and determinations related to potential institutional conflicts with proposed or ongoing research:

- Geisinger's Legal Services Contract Administration database - Institutional relationships with external entities with whom Geisinger contracts to conduct business are maintained in Geisinger's Legal Services Contract Administration database. The database flags contracts that include the opportunity to financially benefit Geisinger (e.g., equity, royalties, licensing).
    - Geisinger Office of Research Compliance receives a weekly database download, which is reviewed to identify relationships related to Geisinger research.
- ORC staff also use this database to identify institutional relationships with external entities when reviewing grant application and research agreement transmittal forms and when creating Research Finance activity accounts for newly awarded research grants and contracts.
- When relationships are identified, they are assessed for potential conflicts of interest by ORC, Geisinger Research Conflict of Interest Committee (RCOIC), and Geisinger Institutional Conflict of Interest Committee (ICOIC), as applicable.
- RCOIC will review the relationship, determine if a potential conflict of interest with research exists and develop a management plan to mitigate any potential conflict on a case-by-case basis, which may include disclosure of Geisinger's relationship with the sponsor in research informed consent forms.
- RCOIC determinations are reported to Geisinger ICOIC
- Management plans are reported to Geisinger ICOIC and IRB

Requirements related to potential conflicts of interest of the institution, its employees and leaders are addressed in the following Geisinger policies:

- Conflict of Interest Policy for Employees and Institutional Conflict
- Conflict of Interest Policy for Directors and Officers

Role of the IRB

While Geisinger RCOIC is responsible for control and management of all research-related conflicts of interest, including development and oversight of a management plan to eliminate, reduce or manage actual or apparent Conflicts of Interest, COI management plans related to human subjects' research for which Geisinger IRB is the IRB of record must be reviewed and approved by Geisinger IRB. All management plans include this stipulation and are reviewed and approved by the convened IRB. The IRB shall consider the COI management plan and may include additional protections to the COI management plan if it deems necessary for the protection of human participants.

While investigator financial disclosures required by Geisinger Policy on Financial Conflicts of Interest in Research trigger RCOIC review and determinations about whether a COI management plan is required, the IRB submission process within iRIS also includes opportunities to identify potential conflicts of interest triggering consultation with ORC and the RCOIC to determine whether a management plan is required. Each IRB submission includes COI attestations by the Principal Investigator related to 1) completion of COI training, 2) completion of annual COI disclosure questionnaire, 3) relationships with study sponsor, 4) existence of a COI management plan, and 5) notification of all study sub-investigators about required training and disclosure requirements. If a management plan related to the study sponsor already exists, the PI is prompted to submit the management plan to the IRB. In addition, completion of Geisinger's annual COI questionnaire IRB is tracked with iRIS. IRB staff triage every IRB submission to ensure all investigators have completed this requirement. If any investigator listed on the study did not complete the most current COI questionnaire, the submission is returned to the PI without review until COI disclosure requirements are complete and the submission returns to the IRB.

The RCOIC determines the existence of institutional conflicts of interest related to research studies on a case-by-case basis. If conflicts are identified, a management plan must be provided to the IRB for review with the related study submission for IRB consideration of potential impacts on the protection of research participants and integrity of the research. If the related research requires informed consent by participants, informed consent language disclosing the relationship must be reviewed and approved by the IRB

3.8 Prompt Reporting for Reportable Events

When conducting human subjects research certain events may occur which require timely notification to the IRB. While these events are not desirable and sometimes unpreventable, investigators must follow the reporting policies within this section to ensure the safety and protection of human participants in their research. Events that may meet the criteria of unanticipated problems involving risk to participants and others and serious or continuing noncompliance are reportable events that require prompt reporting to the IRB. Other events, such as minor protocol deviations or minor noncompliance, do not require prompt reporting to the IRB; however, must still be tracked and documented in the research team's files, and reported to the IRB at the time of continuing review, if applicable.

GIRB uses the following definitions related to reportable events:

1. **Adverse event** is an unfavorable medical occurrence, which may include abnormal signs (for example, abnormal physical exam or laboratory finding), symptoms, or disease, temporally associated with, but not necessarily considered related to the participant's participation in the research study. Note: not all adverse events meet the criteria for prompt reporting to the IRB.
    a. **External adverse event** is an adverse event that occurs at a site where GIRB is not the reviewing IRB, but the event is reported to an investigator (often by a study sponsor) at a site where Geisinger IRB is providing regulatory oversight
    b. **Internal adverse event** is an adverse event that occurs at a site where GIRB is the reviewing IRB

2. **Noncompliance is any failure to follow:**
    a. Applicable federal regulations, state, and local laws, or institutional polices governing human subjects' protections, or
    b. The requirements or determinations of the IRB, including the requirements of the approved investigational plan (i.e., protocol deviations)
        i. **Continuing noncompliance** is a pattern or repeated noncompliance which continues after initial discovery, including inadequate efforts to take corrective actions within a reasonable timeframe
            - **Apparent continuing noncompliance** describes an event that *appears* to constitute noncompliance, and so requires reporting to the IRB for consideration. The term "apparent" is used because the IRB has not yet made a formal assessment of the event
        ii. **Serious noncompliance** is any noncompliance that increases risk of harm to subjects; adversely affects the rights, safety, or welfare of subjects; or adversely affects the integrity of the data and research
            - **Apparent serious noncompliance** describes an event that *appears* to constitute serious noncompliance, and so requires reporting to the IRB for consideration. The term "apparent" is used because the IRB has not yet made a formal assessment of the event

Unanticipated Problem involving risks to participants or others is any incident, experience, or outcome that meets **<u>all</u>** the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied.
- Related, or possibly related to participation in the research (i.e., reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economical, or social harm) than was previously known or recognized.
    a. **Possibly related** means that in the opinion of the investigator, there is reasonable possibility that the incident or outcome may have been caused by the procedures involved in the research

b. **Unanticipated** means unforeseeable at the time of occurrence
c. **Adverse events that are unanticipated problems involving risks to participants or others** are adverse events that require prompt reporting to the IRB as described below; however, most adverse events will not meet the definition of an unanticipated problem, for example, adverse events which are determined by the investigator to be unrelated to the research intervention. Such events do not require prompt reporting.

3. **Reportable event** is any event that requires prompt reporting to the IRB, including apparent serious or continuing noncompliance and unanticipated problems involving risk to participants or others

Principle Investigators are responsible for determining whether an event or incident meets the definition of a reportable event and therefore requires prompt reporting to the IRB. Investigators can contact the IRB office or an IRB Chair for assistance in making these determinations; however, responsibility for making the initial assessment lies with the principal investigator. Examples of reportable and non-reportable events are included at the end of this section.

Incidents of non-compliance that do not meet the IRB reporting requirements (for example, incidents that are not apparent serious or continuing noncompliance and/or unanticipated problems), do not need to be promptly reported to the IRB, but should be documented in a log, in real time, and made available upon request. The IRB expects for investigators to regularly review and monitor noncompliance and protocol deviation logs. A template *Noncompliance/Protocol Deviation Log* is available for investigators to use in existing or modified form. The template is located on the HRPP website. While the template does not need to be used, at minimum, all logs must contain the following information:

- IRB number
- Principal investigator name
- Protocol title
- Participant/subject ID number
- Date of the event
- Date of PI notification
- Description of the event
- Documentation around whether the event is a noncompliance that requires prompt reporting
- Documentation for reporting the event to the sponsor, DSMB or an external group
- Corrective action measures to prevent the event in the future
- Documentation that the PI reviewed the event in the log and the date of his review

Noncompliance/Protocol Deviation Logs are mandatory for:

- Greater than minimal risk studies
- NIH supported research meeting the NIH definition of a clinical trial
- Studies which the funding agency requires reporting

Deviation logs are recommended, but not required for all other studies. Studies requiring a Noncompliance/Protocol Deviation Log must submit them at the time of continuing review. Studies not subject to continuing review requirements must make the logs available upon request.

In overview, GIRB Prompt Reporting Policies require:

1. Prompt reporting of all adverse events and unanticipated events that meet the criteria of an unanticipated problem
2. Prompt reporting of all noncompliance that meet the definition of either an apparent serious noncompliance or apparent continuing non-compliance
3. IRB review and/or determination for all reports of apparent serious or continuing non-compliance and/or apparent unanticipated problems involving risk to participants or others
4. Fulfillment of reporting requirements to all applicable parties and entities (institutional officials, funding agencies, federal agencies, sponsors, etc.)

In addition, events that include an unauthorized disclosure of PHI must also be directly reported to the Geisinger Privacy Office for review, investigation, and recommendations, regardless of whether they meet the definition of a reportable event. This is reported via Privacy Office Incident Reporting Form link in OurGeisinger.

Investigator Reporting Requirements

Investigators must promptly report the following to the IRB on a Prompt Report Form:

1. All internal events meeting the definition of <u>apparent</u> serious or continuing non-compliance
2. All internal events appearing to meet the criteria of an unanticipated problem involving risk to participants or others
3. All external events that:
    a. Impact the rights, safety, and welfare of participants enrolled at a site where Geisinger IRB is providing regulatory oversight for the research, and/or
    b. Present additional serious, unexpected risks to participants enrolled at a site where Geisinger IRB is providing regulatory oversight for the research.

Most adverse events will not meet the definition of an unanticipated problem involving risk to participants or others. Adverse events that do meet these criteria must be reported to the IRB on a Prompt Report Form and are subject to the reporting timeframe described below. Please be aware that some events may meet the criteria for both a serious or continuing non-compliance and an unanticipated problem.

External events and safety reports, which do not impact the rights safety and welfare of, or present additional serious, unexpected risks to participants enrolled at a site under GIRB oversight, do not require prompt reporting to GIRB. Any changes in the research after an external event or safety report must be submitted to GIRB as an amendment for review and approval before implementation, unless fast action is necessary to alleviate immediate hazards to enrolled participants.

Reporting Time Frames

The IRB must receive initial notification of all internal adverse events which are unexpected, fatal, or life threatening, and related or possibly related to the research within 24 hours of discovery.

For all other serious or continuing non-compliance and/or unanticipated problems, initial notification to the IRB must occur within ten working days of the investigator discovering the event.

Prompt Reporting Submission Process

Prompt Reporting means the initial notification of an event to GIRB. The initial notification of a reportable event to GIRB can be completed by sending a high priority email to the Geisinger IRB at irb@geisinger.edu or to any IRB office staff member, or by phone (570-271-8663). These methods can be used when internal adverse events are unexpected, related or possibly related to the research and are either fatal or life threatening and need to be initially reported within 24 hours. These methods can also be used when an investigator needs to collect more information and detail in order to submit a formal Prompt Report Form in iRIS. Such reports must describe the event and all currently known information. It is likely that GIRB will have follow-up questions based on initial reports.

Once all pertinent details have been obtained about the reportable event and there is enough information to submit a formal report, the investigator must submit a Prompt Report Form in iRIS. Any email communications sent as part of an initial notification to the IRB should be included in the iRIS Prompt Report Form.

IRB Responsibilities and Review of Prompt Reports

Prompt Reports are triaged to a qualified member of the IRB office for an initial assessment. The IRB office determines whether the submitted report appears to meet the definition of a serious or continuing noncompliance and/or an unanticipated problem involving risk to participants or others. GIRB staff may contact investigators if the submitted information is incomplete or additional information is required to make the assessment. Staff may also consult with an IRB Chair to help make a determination.

Reports that do not meet the definition of a reportable event are returned with an outcome letter notifying the investigators that the submitted report was determined not be a serious or continuous noncompliance or unanticipated problem. The letter will outline any action items that need to be addressed by the investigator, including summarizing the event at the next continuing review, when applicable.

Reports that meet the definition of a reportable event are assigned to an IRB reviewer and scheduled for review at a convened IRB meeting. All members of the convened committee have access to the Prompt Report Form, the IRB approved study application, protocol, and informed consent document, as well as all other applicable documents (e.g., investigator brochures, instructions for use, etc.). The convened IRB committee discusses the event and related details and makes a determination as to whether allegations of noncompliance meet the definition of serious or continuing noncompliance and/or whether the event meets the definition of an unanticipated problem. The committee also reviews the investigator's proposed corrective action plan and determines if it is adequate or if additional measures should be included. At any point in the review process, a prompt report may be returned to the investigator with questions or requests for additional information or clarifications. This includes tabling a convened review when it is clear additional information is necessary for the committee to make a decision.

Ultimately, the IRB takes whatever actions it deems necessary to address the situations and details described within prompt reports. Examples of actions that might be taken include (but are not limited to):

1. Investigating the event by:
    - Requesting additional records or information about the event and its outcome.
    - Interviewing the involved investigators, research staff, and/or research participants.
    - Interviewing other individuals who may have knowledge of the event.
    - Requesting an independent audit of the event/protocol or of other protocols
2. Implementing Administrative Actions:
    - Requesting the IRB Chair to meet with the involved investigator and/or research staff, and the appropriate department chair to discuss the event/problem
    - Requesting a corrective plan of action and/or written standard operating procedures from the involved investigator and/or his or her department chair
    - Requesting members of the research team to participate in pertinent training and education programs
    - Notifying other organizational entities (e.g., Chief Scientific Officer, Institutional Official, legal counsel, risk management, Chief Privacy Officer, Chief ISO Officer, The Office of Research Compliance, etc.) as necessary.
    - Suspend the principal investigator's privilege to serve as the principal investigator or require a replacement of the principal investigator for the protocol in question
    - Place restrictions on an investigator's privileges to conduct human subjects' research.
3. Require Modifications to the Associated Protocol:
    - Require the principal investigator to provide information about the event to participants currently enrolled in the study
    - Require the investigator to perform additional follow-up or monitoring of the enrolled participants.
    - Shorten study approval period
4. Terminating or Suspending IRB Approval of the Research Study:
    - Identify additional actions the principal investigator or institution should take to protect the rights, safety, and welfare of human participants, such as:
        - Transferring participants to another research study when inclusion and exclusion criteria allow
        - Arrange for clinical care outside the research
        - Require or permit follow-up with participants for safety reasons
        - Notify former and/or current participants of the IRB's decision to terminate or suspend the research
5. Require other actions as determined by the IRB committee
6. Require no further action.

The committee votes on whether reported events constitute serious or continuing non-compliance and/or unanticipated problems involving risks to participants and others, as well as the acceptability of the corrective action measures. The motion and vote are documented in the IRB meeting minutes. If the IRB votes to suspend or terminate the research, the reasons for the suspension or termination are also documented in the IRB minutes.

Reporting IRB Determinations for Prompt Reports

Investigators are notified in writing within ten working days of the IRB's determinations. If the IRB decision requires immediate action on the part of the principal investigator, the determination will be quickly communicated verbally by an IRB Chair to the principal investigator, and then followed with written notification.

In addition to notifying the principal investigator, Geisinger IRB complies with all local, state, and federal regulations for reporting IRB determinations of serious or continuing non-compliance and/or unanticipated problems involving risk to participants or others. Report correspondences are issued within thirty working days to the applicable parties, following a determination from the IRB committee.

The following information is included in all reports sent to the applicable parties:

- Name of the institution conducting the research
- Title of the associated research projects and/or grant proposal
- Name of the principal investigator
- Geisinger IRB number assigned to the research project
- Number of any applicable federal award(s), such as a grant or contract number
- Summary of the research
- Detailed description of the reason for the report
- Actions taken by the institution to address the reported issue (i.e., corrective action plan)

All IRB correspondences related to reportable events are prepared by the Director, IRB Operations and HRPP or his/her designee and then approved by an IRB Chair. Correspondences are signed by at least one IRB Chair.
IRB determinations of serious or continuing non-compliance and/or unanticipated problems involving risks to participants or others will be sent to all applicable parties, which may include:

- Institutional Official(s)
- The Office for Human Research Protections – for federally funded research
- The Food and Drug Administration – for research subject to FDA regulations
- The funding agency and/or the sponsor
- Any other applicable party

Examples

The examples in this section are examples of things that may fit within the defined type of event. Ultimately, each event or incident needs to be examined on a case-by-case basis to determine whet. it is a reportable event which requires prompt reporting. Please remember, some events may constitute more than one type of reportable event, such as a serios non-compliance that also meets the criteria of an unanticipated problem.

Noncompliance/Protocol Deviations not requiring prompt reporting to the IRB

- Obtaining consent using an outdated consent form where there were no substantive differences between the consent form that was used and the consent form that should have been used
- Protocol deviations that do not adversely affect the rights and welfare of human subjects or significantly compromise the quality of the research data

- Performing non-safety related research procedures outside the protocol specified window (i.e., involuntarily administering a questionnaire outside of the protocol window)
- Failure to comply with IRB policies that are administrative in nature, for example, turning in a report of an apparent serious or continuing noncompliance, failure to date consent forms, failure to remove staff from the IRB application, when necessary, etc.,

Serious noncompliance requiring prompt reporting to the IRB

- Failure to obtain prospective IRB approval of the research
- Failure to obtain informed consent from participants or initiating research activities prior to obtaining informed consent
- Enrollment of participants not meeting all eligibility criteria, without sponsor approval
- Failure to follow recommendations of the IRB to ensure the safety of participants
- Failure to report unanticipated problems involving risk to participants and others
- Conducting research activities during a lapse in IRB approval
- Performing research at an unapproved site
- Implementing protocol modifications without obtaining prospective IRB approval
- Altering the informed consent process from that described in the IRB approved protocol
- Obtaining consent with an outdated consent form, when the new consent form contained new information that may have caused the subject to change their mind about participating
- Having research activities performed by individuals who are not sufficiently trained or credentialed to perform the task
- Failure to follow safety monitoring plan
- Not adhering to inclusion/exclusion criteria
- Enrolling more subjects than were approved in the protocol of a greater than minimal risk study
- Any other untoward event that affects the welfare or the privacy, confidentiality or other rights of the research subjects or members of their family (e.g., lost or stolen research data)

Continuing noncompliance requiring prompt reporting to the IRB

- Frequent instances of minor non-compliance (noncompliance that is neither serious nor continuing)
- Failure to respond to a request to resolve an episode on non-compliance
- Repeated failures in securing continuing review approvals resulting in lapses in IRB approval
- Persistence of noncompliance occurring after the implementation of a corrective action plan intended to effectively resolve the noncompliance
- Repeated failure to ensure timely remediation of any non-compliance, identified by or made known to the investigator, with requirements for the conduct of human subjects

Unanticipated problems involving risk to participants or others requiring prompt reporting to the IRB

- Any publications in the literature, safety monitoring report, interim results, or other findings that indicates an unexpected increase in the risk to benefit ratio of the research
- Any complaint from a participant that indicates an unanticipated risk, or which cannot be resolved by the research staff
- Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to research participants
- Mild adverse physical reaction related to participation in a research study that goes beyond the risks stated in the protocol

- Protocol violation (whether intentional or accidental) which deviates from the IRB approved protocol and places participants or others at an increased risk
- A single, 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

3.9 Assurance of Compliance

Geisinger and affiliates covered by the HRPP maintain a Federalwide Assurance under OHRP (45 CFR 46.103), available to investigators and others involved in human subjects research. See Geisinger Federalwide Assurance Statement.

3.10 HRPP Quality Improvement Activities

*Geisinger conducts audits or surveys or uses other methods to assess compliance with organizational policies and procedures and applicable laws, regulations, codes, and guidance and makes improvements to increase compliance, when necessary. (**AAHRPP Element I.5.A**)*

*Geisinger conducts audits or surveys or uses other methods to assess the quality, efficiency, and effectiveness of the Human Research Protection Program and identifies strengths and weaknesses of the Human Research Protection Program and makes improvements, when necessary, to increase the quality, efficiency, and effectiveness of the program. (**AAHRPP ElementI.5.B**)*

Quality Improvement Monitoring

ORC and IRB conduct periodic quality improvement reviews to evaluate adherence to applicable federal regulations, state, and local laws and Geisinger policies and procedures, and to verify research is conducted in accordance with IRB-approved protocols.

Reporting of Quality Improvement Monitoring Results

Results of quality improvement monitoring activities conducted by ORC are documented, summarized, and reported to and reviewed by Geisinger Research Compliance Committee (RCC), Director, IRB

Operations and HRPP, Institutional Official, Research leadership and other units within Geisinger as appropriate. Such quality monitoring activities are also periodically audited by Geisinger Corporate Compliance and Internal Audit. These reports, as well as other institutional monitoring activities relevant to human subjects' research, provide a quantitative and qualitative measurement of compliance with the HRPP and are instrumental in determining ongoing monitoring strategies.

IRB Performance Metrics

The Director, IRB Operations and HRPP produces periodic metrics and analysis of the IRB operations and functions, including detailed measurements of activity volume and processing times.

Based on the results of the assessments and feedback received from the research community, IRB attempts to identify root causes of problems, recommend action plans to correct issues, and provide education, tools, and outreach to promote effectiveness of improvements.

Significant changes to the Human Research Protection Program (HRPP) that are implemented because of the quality assessments are monitored to ensure effectiveness and consistency.

3.11 Investigators' Input to the HRPP

*Geisinger has and follows written policies and procedures so that Researchers and Research Staff may bring forward concerns or suggestions regarding the Human Research Protection Program, including the ethics review process. (**AAHRPP Element I.5.C.**)*

Geisinger HRPP welcomes learning of opportunities for improving processes related to human subjects' research protections, including the IRB review processes and encourages researchers and staff to bring forward any such concerns. The Director, IRB Operations and HRPP reviews suggestions and works with relevant individuals to use to improve HRPP functioning and investigates all concerns and complaints to seek resolution and provide feedback to individuals. The Director, IRB Operations and HRPP may consult with IRB Chair(s), IRB Leadership committee, Research Leadership, and the Institutional Official (IO) as needed for resolution.

Anyone, including Researchers and Research staff, can bring forward questions, concerns and suggestions related to the HRPP and review processes through various channels, including:

- Report possible non-compliance as described in HRPP Handbook, Section 3.8
- Report possible unanticipated problems as described in HRPP Handbook, Section 3.8
- Contact the IRB via Geisinger IRB's general email or telephone, which are regularly monitored
- Use Geisinger internal HRPP SharePoint site link inviting feedback to improve our webpage and services, as well as ask questions, express concerns, and convey suggestions regarding the HRPP
- Use Geisinger.org HRPP webpage "Contact" link to communicate with Geisinger IRB
- Use Geisinger Corporate Compliance Hotline via telephone or web-based reporting service, which can be used for identified or anonymous reporting of concerns
- Offer comments, suggestions and concerns about any matters, issues or processes involving the HRPP, including IRB review and operations to any person in the HRPP / IRB Office, IRB Chair(s), Research leadership, or the Institutional Official (IO).

Section 4 - Knowledge of Human Research Protection Requirements

4.1 Education of Individuals Responsible for Human Research

*Geisinger has an education program that contributes to the improvement of the qualifications and expertise of individuals responsible for protecting the rights and welfare of research participants. (**AAHRPP Element I.1.E**)*

Education and training are provided to all individuals involved with the HRPP. The HRPP Handbook specifies education requirements for IRB members, IRB staff, PI, and key personnel on research studies (*see Section 4.2- Required Training in Human Research Protections*). The HRPP offers comprehensive education to the Geisinger research community.

Education is offered in many areas of research, including ethical standards, related both to research and to professional conduct, Geisinger policies and procedures, and applicable federal, state, and local law. The foundation of ethical training at Geisinger is the Belmont Report, which is made available in required research training and via links on the HRPP/IRB internal SharePoint site and external Geisinger.org HRPP webpage.

HRPP staff develop, facilitate, and provide education for IRB members, IRB staff, researchers, and research staff regarding human research protections.

Training and Education Planning

The Director, IRB Operations and HRPP receives input from Research leadership, IRB Leadership Committee, IRB staff and members, researchers and staff education and training needs. HRPP monitoring, compliance, auditing and evaluation activities, trends in research at Geisinger, and new federal, state, or local regulations and guidance may be considered when planning research educational offerings.

Evaluation of Qualifications

IRB staff

IRB staff qualifications are evaluated during the hiring process, at least annually through Geisinger's performance evaluation processes, and as needed to ensure a high level of functioning within their role. IRB staff job descriptions require obtaining Certified IRB Professional (CIP) or Certified IRB Manager (CIM) certification after meeting the minimum testing requirements.

IRB members

All Primary and Alternate IRB Member qualifications are evaluated by the Director, IRB Operations and HRPP and IRB Chair(s) as part of the IRB member appointment process. Throughout the year, IRB members, including IRB Chair(s), provide feedback to ensure that their service on the IRB contributes to the ethical and regulatory review of research at Geisinger. Annually a formal review of the membership is conducted with the IRB Manager, Director, IRB Operations and HRPP, and IRB Chair(s). The chair(s)

will schedule individual meetings with any member that would benefit from additional one-on-one guidance for further development.

ORC staff

ORC staff qualifications are evaluated during the hiring process, at least annually through Geisinger's performance evaluation processes, and as needed to ensure a high level of functioning within their role. ORC staff are encouraged to obtain Certified Healthcare Research Compliance (CHRC) certification after meeting the minimum testing requirements.

Contributing to the Improvement of Expertise

New IRB staff and members receive mentoring and orientation to Geisinger HRPP. All IRB members and IRB staff receive regular, ongoing training and continuing education.

IRB staff and members are informed of and encouraged to participate in human research protections continuing education opportunities (e.g., regulatory and professional meetings, conferences, webinars, on-demand learnings).

Before IRB members can serve as an independent reviewer, they must complete all the necessary training through Geisinger-required CITI courses (Protection of Human Research Subjects, Responsible Conduct of Research and Good Clinical Practice), GIRB orientation and GIRB Mentor-Mentee program.

Educational Materials and Resources

The Geisinger research community, IRB members, IRB staff and other individuals responsible for the protection of human research participants have access to educational materials, available online and in printed format, or offered as courses or workshops. This includes:

- Geisinger's Human Research Protection Program's internal and external webpages, with links to Geisinger's HRPP Handbook and Guidance, instructional information, FAQs, topical educational materials, archived presentations, forms and templates.
- Access to required training through interactive online Collaborative Institutional Training Initiative (CITI) Courses: Protection of Human Research Subjects, Responsible Conduct of Research and Good Clinical Practice
- iRIS submission system, provides instructional text and explanations throughout the Study Application
- iRIS training manuals

4.2 Required Training in Human Research Protections

*Geisinger has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board, as appropriate. (**AAHRPP Element I.1.D**)*

Geisinger's Research Education and Training Policy applies to all investigators and members of the research staff (including persons not employed by Geisinger but conducting research at a Geisinger entity), non-traditional research personnel (including persons such as students, volunteers, or interns), compliance committee members, HRPP staff, IRB members. This policy outlines research training requirements that must be completed through the Collaborative Institutional Training Initiative (CITI) online platform. The following training courses must be completed and are valid for three (3) years: 1) Human Subjects & Data Only Researchers & Staff, IRB Members & Staff, 2) RCR for Researchers, Research Staff, and Administrators, and 3) Good Clinical Practice.

CITI Program course completion records are securely and automatically downloaded into iRIS user accounts daily. This automation permits the iRIS system to validate training during every iRIS submission (except for Prompt Reports, Final Reports and Research Determination Worksheet Study Applications). The program also emails automatic scheduled training expiration notifications to users.

ORC staff monitor CITI expired training reports monthly, use them to remind researchers and staff of the training requirements. If training is not completed or the PI does not remove the individual(s) with expired training from the study via submission of a Key Study Personnel amendment to the IRB within the next month, IRB staff is notified. Designated IRB staff follows up with the PI and individual(s) with expired training to reconcile this issue. If not reconciled …

Section 5 - Research with Drugs, Devices, Biologics

FDA regulates clinical investigations (research) "that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, dietary supplements that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products." (See 21 CFR 56.101). All research involving investigational or unlicensed test articles must be conducted in accordance with FDA requirements for informed consent and IRB review, regardless of funding source or sponsor.

This section outlines the policy for:
research using investigational drugs, devices, or biologics
research with FDA-approved drugs, approved/cleared devices, or licensed biologics (sometimes called "commercially available")
sponsor-investigator research
radioactive materials
handling (inventory control and storage) of investigational drugs, devices, or biologics
emergency, humanitarian, or compassionate use of investigational drugs, devices, or biologics

5.1 Research with Test Articles

*When research involves investigational or unlicensed test articles, Geisinger confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval. (**AAHRPP Element I.7.A**)*

Research with FDA-regulated test articles may commence only after the IRB has approved the protocol and:

- receives documentation that the research will be conducted under an applicable Investigational New Drug Application (IND) or Investigational Device Exemption (IDE); or
- formally determines and documents that the proposed use of any investigational device satisfies the FDA criteria for non-significant risk devices; or
- formally determines that satisfactory justification has been provided by the investigator as to why an IND or IDE is not required.

DEFINITIONS:

Biologic: A biological or related product, regulated by the FDA, including blood, vaccines, allergenics, tissues, and cellular and gene therapies. Biologics, in contrast to drugs that are chemically synthesized, are derived from living sources (such as humans, animals, and microorganisms). Studies of unlicensed biologics are regulated according to the IND regulations, except in some cases when the biologic is in a combination product with a medical device. FDA regulates biologics general use and licensing under 21 CFR 600 and 601 (42 U.S.C 262) of the Public Health Service Act.

Clinical investigation: 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 (FD&C Act), or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an

application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part. (See 21 CFR 56.102)
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. (See 45 CFR 46.102)
Combination product: A product containing a combination of a drug, a device, or a biological product. Studies of combination products are regulated according to the IND or IDE regulations, depending on the components of the product. The FDA determines which of its organizational components has primary authority for the premarket review and regulation of products that are comprised of any combination of a drug, device, and/or biological. (See definitions and regulations at 21 CFR 3.2(e))
Human subject*:* An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient. (See 21 CFR 56.102)
Off-Label: Use of an approved drug, an approved or cleared device, or a licensed biologic for an indication not in the approved labeling. Most research involving off-label uses requires IND or IDE applications. (See *FDA Information Sheet – "Off-Label" and Investigational Use of Marketed Drugs, Biologics and Medical Devices – Guidance for Institutional Review Boards and Clinical Investigators)*
Test article*:* Any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act. (See 21 CFR 56.102)

Research with Drugs

*When research involves investigational or unlicensed test articles, Geisinger confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval. (**AAHRPP Element I.7.A**)*

Clinical investigations of drugs are subject to the Investigational New Drug Application (IND) regulations, 21 CFR 312.
An investigational drug must have an IND granted by the FDA before it can be shipped, unless one of the exemptions outlined in 21 CFR 312.2 is met.
Study Applications for research investigating a drug must include a valid IND number unless that research is exempt from the IND regulations. The IND number must either match the number on the sponsor-written protocol with the same title as the proposed research, communication from the sponsor specific to the proposed research, or communication with the FDA. IND numbers may not be validated with an Investigator Brochure (which may serve multiple INDs). The IND number will be required prior to the IRB approval of the proposed research.
21 CFR 312 outlines the following exemptions to the IND regulations when conducting research with drugs:
Exemption 1
As stated in 21 CFR 312.2(b), clinical investigation of a drug is exempt from the IND regulations
if the drug is lawfully marketed in the United States and all the following are true:

- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.
- If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product.
- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

- The investigation is conducted in compliance with the requirements of 21 CFR 312.4 and 21 CFR 312.8 (Promotion and Charging for investigational drugs).

Exemption 2

- A clinical investigation is for an in vitro diagnostic biological product that involves one or more of the following:
    - Blood grouping serum.
    - Reagent red blood cells.
    - Anti-human globulin.
- The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.
- The diagnostic test is shipped in compliance with 21 CFR312.160.

Exemption 4

- A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

See FDA guidance for FDA's current thinking on exemptions from IND requirements:

- Guidance for Clinical Investigators, Sponsors, and IRBs Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND
- Guidance for Industry IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer

Research with Devices

*When research involves investigational or unlicensed test articles, Geisinger confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval. (**AAHRPP Element I.7.A**)*

Clinical investigations of devices are subject to the Investigational Device Exemptions (IDE) regulations, 21 CFR 812. An approved investigational device exemption (IDE) permits a device that is not approved (via premarket authorization, PMA) or cleared to market (via 510(k)) by the FDA to be shipped to conduct clinical investigations of that device. Significant risk investigational devices must have an IDE issued by FDA before they can be shipped. Non-Significant risk devices are considered to have an approved IDE when the IRB agrees with the sponsor that the device meets the criteria for a non-significant risk device.

Research with devices falls into three categories:
Investigations of significant risk devices to determine safety and effectiveness of the device
Investigations of Non-Significant risk devices to determine safety and effectiveness of the device
Investigations exempted from the IDE regulations
Studies that include medical device use in an incidental way, where the device or the use of the device is not the focus of the research, are generally not considered to be FDA-regulated research or subject to 21 CFR 812, and in some instances are eligible for IRB review according to the expedited procedure.

Significant Risk Device Research

Applications for research on the use of a significant risk device must be accompanied by documentation from the FDA that includes a valid IDE number. The IDE number must match the number on the sponsor protocol with the same title as the proposed research, be listed on communication from the sponsor specific to the proposed

research, and on communication with the FDA. IDE numbers may not be validated with a device manual (which may serve multiple IDEs).

Significant risk device means an investigational device that (21 CFR 812.3(m)):

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

Non-Significant Risk Device Research

When research is conducted to determine the safety or effectiveness of a device, the organization confirms that the device fulfills the requirements for an abbreviated IDE (21 CFR 812.2(b)(1)). 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:

- The device is not a banned device.
- The sponsor labels the device in accordance with 21 CFR 812.5;
- The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device and maintains such approval.
- The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, consent under 21 CFR 50 and documents it, unless documentation is waived;
- The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations;
- The sponsor maintains the records required under 21 CFR 812.140(b) (4) and (5) and makes the reports required under 21 CFR 812.150(b) (1) through (3) and (5) through (10);
- The sponsor ensures that participating investigators maintain the records required by 21 CFR 812.140(a) (3) (i) and make the reports required under 21 CFR 812.150(a) (1), (2), (5), and (7);
- The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

If the investigator applies to the IRB for a Non-Significant risk determination for a device study, but the IRB determines that the device is significant risk, the IRB shall notify the investigator and the sponsor, if appropriate. The outcome of the review of the research study will be deferred until the investigator and/or sponsor receives documentation from the FDA on the status of IDE.

Exempt Device Research

Clinical investigations that are exempt from IDE regulations still require IRB review and approval. An investigation of a medical device in human subjects research that is exempt from the IDE regulations must fall into one of the following categories (Criteria in 21 CFR 812.2(c)):

- 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.
- A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

- A diagnostic device (that is, an in vitro diagnostic device) if sponsor complies with applicable labeling requirements in 21 CFR809.10(c) and if the testing:
    - Is noninvasive,
    - Does not require an invasive sampling procedure that presents significant risk,
    - Does not by design or intention introduce energy into a subject, and
    - Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- 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.
- 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.

In Vitro Diagnostic Device Research

The U.S. Food and Drug Administration (FDA) has defined in vitro diagnostic products as those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, 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)).

FDA Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable explains that the FDA will exercise enforcement discretion (choose not to enforce a regulation) with respect to its current regulations governing the requirement for informed consent when left-over, non-identifiable human specimens are used for FDA regulated in vitro diagnostic (IVD) device investigations. If specific conditions (described below) are met, FDA does not intend to object to the use, without informed consent, of leftover human specimens – remnants of specimens collected for routine clinical care or analysis that would otherwise have been discarded – for in vitro diagnostic device investigations that meet the criteria for exemption from the Investigational Device Exemptions (IDE) regulation at 21 CFR 812.2(c)(3) as long as subject privacy is protected by using only specimens that are not individually identifiable. FDA also includes in this policy specimens obtained from specimen repositories and specimens that are left over from specimens previously collected for other unrelated research if these specimens are not individually identifiable.
FDA will only exercise such enforcement discretion, and thus not require informed consent, if all the following are true:

- The investigation meets the IDE exemption criteria at 21 CFR 812.2(c)(3).
- The study uses leftover specimens, that is, remnants of specimens collected for routine clinical care or analysis that would have been discarded. The study may also use specimens obtained from specimen repositories or leftover specimens that were previously collected for other research purposes.
- The specimens are not individually identifiable, i.e., the identity of the subject is not known to and may not be readily ascertained by the investigator, or any other individuals associated with the investigation, including the sponsor. If the specimen is coded, it will be considered to be not individually identifiable if neither the investigator(s) nor any other individuals associated with the investigation or the sponsor can link the specimen to the subject from whom the specimen was collected, either directly or indirectly through coding systems.
- The specimens may be accompanied by clinical information if this information does not make the specimen source identifiable to the investigator or any other individual associated with the investigation, including the sponsor.
- The individuals caring for the patients are different from those conducting the investigation and do not share information about the patients with the investigator(s).

- The specimens are provided to the investigator(s) without identifiers and the supplier of the specimens has established policies and procedures to prevent the release of personal information**.**
- The study has been reviewed by an IRB in accordance with 21 CFR 56, except for the informed consent requirements described there.

Studies that do not fall within the intended enforcement discretion expressed in the FDA guidance would require informed consent of subjects. Such studies include, but are not limited to, those where any of the following conditions apply:

- The study does not meet the IDE exemption criteria at 21 CFR 812.2(c)(3);
- The specimens are individually identifiable, i.e., the identity of the subject is known to or may be readily ascertained by the investigator, or any other individuals associated with the investigation, including the sponsor.
- The specimens were collected specifically for the proposed investigation. That is, the specimens are not leftover from routine clinical care or analysis or leftover from other research.
- The amount of specimen needed for the study is more than would be left over from what is usually collected for routine clinical analysis, or
- The test results will be reported to the subject's health care provider. For example, during comparative studies involving Bacillus anthracis detection devices, it would be inappropriate not to report positive results if they occur in the course of an investigation.

In vitro diagnostic (IVD) device research is still subject to FDA regulations governing research with humans. Therefore, investigators who propose to conduct such research must submit an IRB protocol. The protocol must also provide information to support the seven findings, as described above, that the IRB must make. As with other investigational device studies, the investigator must submit all relevant supporting documents from the sponsor, including the investigator brochure, with the study submission.

Additional details can be found in the following guidance documents:

- Geisinger Guidance Document - Significant Risk (SR) and Non-Significant Risk (NSR) Medical Device Studies
- FDA Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors - Frequently Asked Questions About Medical Devices
- FDA Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors - Significant Risk and Non-Significant Risk Medical Device Studies

Studies that include medical device use in an incidental way, where the device or the use of the device is not the focus of the research, are generally not considered to be FDA-regulated research or subject to 21 CFR 812, and in some instances are eligible for IRB review according to the expedited procedure.

5.2 Radiology Devices and Radioactive Materials

*When research involves investigational or unlicensed test articles, Geisinger confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval. (**AAHRPP Element I.7.A**)*

The FDA regulates radiology devices and radioactive materials used in research. Oversight at Geisinger is handled by the Radiation Safety Committee (RSC). See Geisinger Policy - Human Research Using Radiation Sources.

When a radiopharmaceutical cannot be classified as "generally recognized as safe and effective," the RSC may not approve the protocol, and an IND may be needed. Human research projects involving radiation are regulated by State or Federal agencies depending on the radiation source.

Prior to using radiation that is not part of usual care in human research, the principal investigator (PI) must receive project approval from the Geisinger Radiation Safety Committee (RSC) and the Institutional Review Board (IRB). The RSC documents its review and approval of protocols and informed consent language for research using such radioisotopes or radiation machines. A copy of the approval letter/correspondence must be uploaded with the protocol submission to the IRB. Without this approval, a study which employs these modalities cannot be approved.

5.3 Research with Biologics

*When research involves investigational or unlicensed test articles, Geisinger confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval. (**AAHRPP Element I.7.A**)*

Clinical investigations of biologics are regulated in the same way as clinical investigations for drugs, subject to 21 CFR 312, unless the biologic is part of a combination product that the FDA has assigned for premarket approval to the Center for Devices and Radiological Health (CDRH). In such cases, the biologic/device combination product would require an IDE prior to research approval by the IRB.
Geisinger, through the Institutional Biosafety Committee (IBC), assumes responsibility for reviewing all proposed research activities involving recombinant DNA, biohazardous material and select agents and toxins conducted under the auspices of Geisinger.
Geisinger policy requires that all investigators conducting research activities involving recombinant DNA, biohazards (including commercial cell lines, cell lines from outside investigators, human tissue, cells or blood or other potentially infectious materials) or select agents and toxins must obtain approval for such activities from the IBC prior to initiating the project. Without this approval, a study using these products cannot be approved by the IRB.

5.4 Sponsor-Investigator Research

*When research involves investigational or unlicensed test articles, Geisinger confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval. (**AAHRPP Element I.7.A**)*

*Geisinger has and follows written policies and procedures to ensure that the handling of investigational or unlicensed test articles conforms to legal and regulatory requirements. (**AAHRPP Element I.7.B**)*

During the submission and review of the billing determination of research involving test articles, OSP staff identify whether a Geisinger investigator holds his/her own IND or IDE. ORC staff review the research before IRB submission and may assist the investigator in understanding sponsor-investigator responsibilities.

Sponsor-investigators who submit protocols to the IRB involving FDA test articles must include all supporting FDA documentation for the IND or IDE and any Geisinger required approvals for applying for an IND or IDE.

The IND product must be stored, secured, dispensed, and documented in accordance with the Geisinger Investigational Pharmacy policies. *(See Section 5.5 - Internal Handling of Test Articles).*
Prior to approving a protocol that involves a sponsor-investigator, the IRB must be satisfied that the sponsor-investigator is knowledgeable about his/her responsibilities and has adequate procedures in place to comply with the FDA regulatory requirements. An on-site compliance review, designed to evaluate compliance with the FDA regulatory requirements, may be conducted by ORC as a condition for approval of the protocol by the IRB.

Investigator-held INDs
A sponsor-investigator for an IND protocol must follow the FDA regulations in 21 CFR 312 applicable to sponsor responsibilities.
See Geisinger guidance, Sponsor-Investigator Research when the Geisinger investigator holds the IND.

Investigator-held IDEs - Significant Risk Devices
A sponsor-investigator for an IDE protocol must follow the FDA regulations in 21 CFR 812. See Geisinger guidance, Sponsor-Investigator Research when the Geisinger investigator holds the IDE.

Non-Significant Risk Device Studies when Investigator Acts as Sponsor
Investigators studying non-Significant devices, regulated by the abbreviated IDE regulations, have abbreviated sponsor responsibilities when there is no industry sponsor. See the following guidance documents:

- Significant Risk (SR) and Non-Significant Risk (NSR) Medical Device Studies
- Sponsor-Investigator Research Requirements (when a Geisinger investigator is the sponsor of a non-significant risk device clinical investigation).

5.5 Internal Handling of Test Articles

*Geisinger has and follows written policies and procedures to ensure that the handling of investigational or unlicensed test articles conforms to legal and regulatory requirements. (**AAHRPPElementI.7.B**)*

Geisinger policy, Investigational Drugs, was established to protect the safety of patients participating in investigational or clinical medication studies by providing a process for the safe and appropriate use of investigational drugs within the Geisinger Health System (GHS).
Any protocol involving the administration of an investigational drug or investigational new drug to human research subjects must have, as a condition of approval, an IDS Authorization Number from the IDS Pharmacy. This Authorization Number provides the IRB with evidence that a drug review has been performed for the protocol, including any potential impact on the IDS Pharmacy; dosing issues; reimbursement issues; assessment of staff's knowledge of proper drug storage, labeling, record-keeping, security, etc.; assessment of the site's ability to meet these requirements; and determination of the IDS Pharmacy's role, if any. As part of this process, the PI (or designee) will supply to the IDS Pharmacy the current copy of the protocol and Investigator's Drug Brochure(s) (if applicable).

Investigational devices that are under the control of principal investigators which are used at Geisinger must be procured, stored, secured, dispensed, used, and monitored in accordance with specific device requirements as detailed by the sponsor.

Geisinger IBC is responsible for review and approval of all proposed handling of investigational biologics used in research conducted at Geisinger to ensure compliance with regulatory requirements. IBC approval must be submitted to the IRB with study applications including the use of investigational biologics.
For clinical investigations, Geisinger promotes researchers' adherence to ICH guidelines as adopted by the FDA in the form of the **E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) | FDA**.

5.6 Other Access to Investigational Drugs and/or Devices

The FDA may make an unapproved drug/device available under several mechanisms:

- Emergency Use
- Compassionate Use (or Single Patient/Small Group Access)
- Treatment Use (Larger Group/More Widespread Use)
- Continued Access
- Humanitarian Use Devices (HUDs)
- Orphan Drugs

DEFINTIONS (per 21 CFR 312.300):

Expanded access: Use of investigational new drugs and approved drugs where availability is limited by a risk evaluation and mitigation strategy (REMS) when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. The aim of this subpart is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition. [21 CFR 312.300 (Subpart I)]
***Expanded Access Programs (EAPs)*:** The FDA uses this term to refer to the various types of allowable expanded access use.
Immediately life-threatening disease or condition: A stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.
***Orphan drug*:** A drug intended for use in a rare disease or condition 21CFR316
Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

Emergency Use of a Test Article

*Geisinger has and follows written policies and procedures for compliance with legal and regulatory requirements governing emergency use of an investigational or unlicensed test article. (**AAHHRPP Element I.7.C**)*

Emergency Use of a test article is exempt from prior IRB review and approval, provided that such emergency use is reported to the IRB within five working days *after the use*. Expedited IRB approval is not permitted in emergency use. Investigators should contact the IRB about his/her intent to use a test article in an emergency or to invoke the exception to the requirement to obtain consent. A senior staff member in the Institutional Review Board Office will advise whether the circumstances follow FDA regulations.

Definitions:
***Emergency Use*:** Use of a test article on a human participant in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(d)).

Life-threatening includes both life-threatening and severely debilitating:

- ***Life-threatening**:* Diseases or conditions where likelihood of death is high unless the course of the disease is interrupted, and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened IRB meeting is feasible.
- ***Severely debilitating**:* Diseases or conditions that cause major irreversible morbidity e.g., blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis, or stroke.

Test Article: Any drug, biological product, or medical device for human use [21 CFR 56.102(1)]. Specific additional requirements apply; see Guidance Emergency Use of a Test Article.

Specific additional requirements apply; see Guidance Emergency Use of a Test Article.

For research subject to FDA regulations, the emergency use of a test article, other than a medical device, is a clinical investigation, the patient is a participant, and the FDA may require data from an emergency use to be reported in a marketing application. DHHS regulations do not permit data obtained from patients to be classified as human participants research, nor permit the outcome of such care to be included in any report of a research activity subject to DHHS regulations.

To use a test article in a life-threatening situation without prior IRB approval:

- The participant is in a life-threatening or severely debilitating situation.
- No standard acceptable treatment is available.
- There is not sufficient time to obtain IRB approval.
- The use is reported to the IRB within five working days.
- Any subsequent use of the test article is subject to IRB review.
- If the research involves an investigational drug, the FDA has issued an IND.
- **Informed Consent** will be obtained in accordance with FDA regulations, or the circumstances meet the exception to the requirement for consent in FDA regulations.
    - Informed consent is sought from each prospective participant or the participant's legally
    - authorized representative, in accordance with and to the extent required by 21 CFR 50 and informed consent is appropriately documented, in accordance with and to the extent required by 21 CFR 50.27; OR
    - The following requirements from exception from informed consent are satisfied:
        - BEFORE use of the investigational article

        - The investigator and an independent physician, who is not otherwise participating in the clinical investigation, certify in writing:
            (1) The patient is confronted by a life-threatening or severely debilitating situation, necessitating the use of the test article
            (2) Informed consent cannot be obtained from the patient (because the patient cannot communicate or is incompetent to give consent)
            (3) Time is not sufficient to obtain consent from the patient's legally authorized representative
            (4) No alternative method of approved or recognized therapy is available that provides an equal or greater likelihood of saving the patient's life, OR
    - AFTER use of the test article the following is completed and documented:
        - In the investigator's opinion, immediate use of the test article was required, and time was not sufficient to obtain the independent physician determination
        - Within five working days after the use of the article, have the determination above (1-4) reviewed and evaluated in writing by an independent physician.
- **Submission to the IRB** - Report to the IRB within 5 days the emergency use. The following should be submitted to the IRB within iRIS:
    - Emergency Use Notification Form
    - Documentation obtained prior to the emergency use:
        - Copy of the signed informed consent document (unless FDA requirements for exception from informed consent are met - 21 CFR 50.23
        - IRB Chair review and acknowledgement of the emergency use
        - Assessment of the patient's condition and need for emergency use by an independent, uninvolved physician
        - Authorization from the drug or device manufacturer
        - Communications from the FDA
        - Approval from the clinical department/service line leadership, if applicable
- **IRB Review (Retrospective)**
    - An IRB Chair or designated IRB member reviewer will review the iRIS documentation submitted. IRB review includes an assessment of if the conditions for the emergency use were satisfied. The reviewer completes an iRIS reviewer sheet, and an official letter of outcome is sent to the PI and study contact. If the emergency use did not meet the criteria allowing an exemption from prior IRB review and approval, the action will be handled according to HRPP non-compliance process.
    - All relevant documentation on emergency uses of test articles must be maintained by the PI as well as in the IRB records within the iRIS electronic IRB system.
- **Reporting to the FDA**
    - Drugs – Physician or sponsor must submit an expanded access submission to FDA within fifteen working days of FDA's authorization of the use. [21 CFR 312.310]

Devices without an IDE - Physician must report the use to FDA (CDRH or CBER) within five working days after the use.

- Devices with an IDE - IDE sponsor must report the use to FDA within five working days from the time the sponsor learns of the use.

Expanded Access to Investigational Drugs and Devices for Treatment Use

Expanded access is a means by which manufacturers make investigational new drugs available, under certain circumstances, to treat a patient(s) with a serious disease or condition who cannot participate in a controlled clinical trial.
Most human use of investigational new drugs takes place in controlled clinical trials conducted to assess the safety and efficacy of new drugs. Data from these trials are used to determine whether a drug is safe and effective and serve as the basis for the drug marketing application. Sometimes, patients do not qualify for these controlled trials because of other health problems, age, or other factors, or are otherwise unable to enroll in such trials (e.g., a patient may not live sufficiently close to a clinical trial site).

For patients who cannot participate in a clinical trial of an investigational drug but have a serious disease or condition that may benefit from treatment with the drug, FDA regulations enable manufacturers of such drugs to provide those patients access to the drug under certain situations, known as "expanded access." For example, the drug cannot expose patients to unreasonable risks given the severity of the disease to be treated and the patient does not have any other satisfactory therapeutic options (e.g., an approved drug that could be used to treat the patient's disease or condition). The manufacturer must also be willing to make the drug available for expanded access use. The primary intent of expanded access is to provide treatment for a patient's disease or condition, rather than to collect data about the drug.

Expanded access to investigational drugs and devices requires prior IRB review and approval (except for Emergency Use – (*See Section 5.7- Other Access to Investigational Drugs and/or Devices*).

There are three categories of expanded access program (EAP) for investigational drugs:

5.6.1.1 Single patients, including for emergency use, (21 CFR 312.310)
5.6.1.2 Intermediate-size patient populations (21 CFR 312.315)
5.6.1.3 Treatment IND or "treatment protocol" for widespread treatment use (21 CFR 312.320)

See Guidance Expanded Access Program (EAP) for Drugs.

Orphan Drugs

The Orphan Drug Designation program provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S. These drugs are not expected to recover the costs of developing and marketing as treatment drugs.

Humanitarian Use Device (HUD)

Definitions:

***Humanitarian Use Device (HUD)*:** A device intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 8,000 individuals in the United States per year.
***Humanitarian Device Exemptions (HDE)*:** Issued by the FDA; an approved HDE authorizes marketing of the HUD.

A Humanitarian Use Device (HUD) is a device intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 8,000 individuals in the United States per year. Humanitarian Use Devices are regulated under 21 CFR 814 (Subpart H). While HUD use is not considered "research", FDA regulations require IRB approval of a HUD before use. For research under a HDE, the scope of the IRB approval is to confirm the planned use is consistent with the FDA-approved indication for the HDE.

Applying to the FDA for a Humanitarian Device Exemption (HDE)

To obtain approval for an HUD, an HDE application is submitted to FDA. The HDE application:

- *Must contain* sufficient information for FDA to determine that:
  - The device does not pose an unreasonable or significant risk of illness or injury, and
  - The probable benefit to health outweighs the risk of injury or illness from its use, considering the probable risks and benefits of currently available devices or alternative forms of treatment.
- *Is not required to contain* the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose.

Criteria for HUD Use

Clinical (non-research) use of HUDs:

- HUDs can only be used after IRB approval has been obtained for the use of the device for the FDA approved indication (except Emergency Use). New HUD use applications are submitted via iRIS new study submission for review by the convened IRB.
- HUD use is subject to continuing review and approval by the IRB; if applicable, the expedited procedure may be used at continuing review.
- An IRB-approved consent form is not required.
- To use a HUD for a new indication, a new designation of HUD status must be obtained (i.e., a new HDE submitted to the FDA); see 21 CFR 814.110.

Investigational (research) use of a HUDs:

- Researchers who want to study a HUD for a new indication must submit an IDE application to FDA if the device is a significant risk device.
- The investigational use of a HUD under these circumstances is a clinical investigation and must be conducted as an investigational device (IDE) in accordance 21 CFR 812, 50, 54, and 56.

Resources: Regulations and FDA Guidance

- Guidance - Humanitarian Use Device
- 21 CFR 814 (Subpart H) Humanitarian Use Devices
- Humanitarian Device Exemption
- HDE Approvals
- Humanitarian Device Exemption (HDE): Questions and Answers Draft Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff (Draft Guidance)
- Humanitarian Device Exemption (HDE) Program Guidance for Industry and Food and Drug Administration Staff

Planned Emergency Research

Planned Emergency Research: Planned research in life-threatening emergent situations where there is an exception for obtaining prospective informed consent. (21 CFR 50.24)

The conduct of planned research in life-threatening emergent situations where obtaining prospective informed consent has been waived, is provided by 21 CFR 50.24. The research plan must be approved in advance by FDA and the IRB, and publicly disclosed to the community in which the research will be conducted. Public disclosure following the completion of the study to apprise the community and researchers of the study results is also required.

In accordance with 21 CFR 50.24, the IRB may approve planned research in an emergency setting without the informed consent of the participants or their legally authorized representatives in a limited class of emergency situations when the following criteria are met and documented:

- Potential subjects are in a life-threatening situation, and
  - available treatments are unproven or unsatisfactory and
  - collection of scientific data is required to determine the safety and effectiveness of the experimental intervention
- Obtaining informed consent is not feasible because:
  - the potential subject is not able to consent due to his/her medical condition
  - the intervention must be administered before consent from the potential subject's authorized representative is feasible and
  - there is no reasonable way to prospectively identify potential eligible subjects
- Participation in the research study holds out the prospect of direct benefit to the subjects because:
  - the subjects are facing a life-threatening situation
  - appropriate pre-clinical and prior clinical research studies support the potential for direct benefit and
  - the risks associated with the research are reasonable relative to the risks of the subjects' condition and the risk/benefit ratio of standard therapy for the condition
- The research could not be practicably carried out without the waiver.

For more information, see 21 CFR 50.24 and Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors Exception from Informed Consent Requirements for Emergency Research.

Investigators involved in the development or implementation of such research studies, should contact the IRB Office as early as possible in the protocol development process for assistance with this matter.

Section 6 - Structure and Composition of the IRB

6.1 Scope of IRB Authority

Geisinger established the IRB and grants the IRB committee the authority to approve, require modifications to secure approval, and disapprove all research activities overseen and conducted by Geisinger. The IRB committee has the authority to act independently to bind all activities falling under their purview to their decisions. No Geisinger institutional official or committee may approve human research that was not approved by the IRB. Additionally, the IO issues a direct, written delegation of authority under an Institutional Charge to IRB members upon appointment to the IRB (see Charge to IRB members). The IO in turn has the authority delegated to him or her from the Geisinger Chief Executive Officer (CEO).

Individuals with competing business interests or individuals responsible for business development (e.g., vice president for research, director of grants and contracts) may not serve as IRB members and may not carry out the day-to-day operations of the review process.

Specific authority granted to the IRB includes: approval, required modifications, or disapproval of all human research activities overseen and conducted by the investigators/research team; monitoring the consent process and the conduct of the research; and suspension or termination of approval of research that is not conducted in accordance with regulatory or institutional requirements or that has resulted or may result in unexpected serious harm to human subjects, even if previously approved. The IRB also has the authority to observe or monitor any human research to whatever extent it considers necessary to protect research participants. 45 CFR 46.108, 46.112, and 46.113) The IRB investigates allegations of non-compliance with human subjects' regulations and reports of unanticipated problems. In cases where corrective action is needed, the IRB issues appropriate sanctions including but not limited to requesting changes, determining data collected cannot be used for publication, suspending or terminating approval, recommending additional education in the protection of human subjects in research, disqualifying investigators from conducting research involving human subjects at Geisinger, and recommending that further administrative action be taken.

With applicable approvals and written agreements, Geisinger may also use the IRB of another organization to ensure effective and timely research review.

Upon request, or as needed, the IRB shall review and comment on proposed external regulations dealing with human research. When appropriate, the IRB will formulate draft policies and procedures for approval by the IO.

Decisions of the IRB

IRB approval is always necessary before a research project involving human subjects may begin. An IRB decision to not approve a human research project, or require modifications as a condition for approval, cannot be overturned and approved by any Geisinger official or committee.

The IRB must provide the investigator with a written statement of the reasons for not approving proposed research and must give the investigator an opportunity to respond in person or in writing. The IRB must carefully and fairly evaluate the investigator's response in reaching a final determination.

Appeal Process

If an investigator has concerns with respect to procedures or decisions of the IRB, he/she is encouraged to discuss the concerns with the IRB Chair(s) and/or Director, IRB Operations and HRPP; however, no further action on the submission can be taken until the investigator submits his/her concern(s) in writing that would include a justification for changing the IRB decision. The IRB reviews the request using the standard procedures. If the concerns are not satisfactorily resolved, a factfinder could be appointed to review the matter and report back or the IRB could seek assistance from consultants or internal administrative units such as Internal Audits or the Department of Legal Services.

Reporting Obligations within Geisinger

The IRB is supported by the Office of the Institutional Review Board and reports up through Research Administration leadership to the IO. The IO is the institutional official responsible for assuring compliance with Geisinger policies and external regulations related to human subjects' research and assures that human subjects research to which the FWA applies is conducted in accordance with the terms of assurance. The IO reviews periodic reports regarding IRB activities and meets quarterly with Director, IRB Operations and HRPP and Research leadership to discuss current state of the IRB, human subjects research activity, and address any questions or concerns. All incidents of serious or continuing non-compliance or unanticipated problems involving risks to participants are reported to the IO and Research leadership.

Responsibilities to Regulatory Agencies

The IRB must comply with the requirements of all relevant federal regulatory and compliance enforcement agencies or offices, including OHRP and FDA, as well as relevant agencies of the State of Pennsylvania.

6.2 Relationships between the IRB and External Entities

There are occasions when direct communication between the IRB and the sponsor may facilitate resolution of concerns about study procedures or specific wording in an informed consent document. The IRB staff may engage in such direct communication on behalf of the IRB when the IRB Chair or the Director, IRB Operations and HRPP considers it desirable. The clinical investigator will be kept apprised of such communication.

For FDA-regulated research, clinical investigators serve as the link between the IRB and the sponsor and are required to do so by the FDA in compliance with his/her obligations as clinical investigators. This relationship is agreed to by investigators when they sign the Statement of Investigator Form FDA 1572 (for investigational drug and biologic studies with an IND) or an investigator agreement (for investigational device studies with an IDE).

The FDA indicates that direct communication between the sponsor and the IRB may be appropriate when the IRB does not accept a sponsor's Non-Significant Risk (NSR) designation of a medical device (21 CFR 812.66). Direct communication between the sponsor and the IRB is required for the waiver of informed consent in planned emergency research relative to (a)the public disclosures required; or (b) disapproval of such a waiver under 21 CFR 50.24(e). *(*See *Section 5.4 - Sponsor-Investigator Research)*

6.3 IRB Composition and Membership

*The IRB has qualified leadership (e.g., chair and vice chair) and qualified members and staff. Membership and composition of the IRB are periodically reviewed and adjusted as appropriate. (**AAHRPP Element II.1.B**)*

The IRB has a qualified Chair and/or Co-Chair(s), members (primary and alternate), and staff whose membership and composition is reviewed and adjusted annually by the Director, IRB Operations and HRPP in collaboration with the IRB Chair(s) and approval by the Institutional Official (IO). This review ensures that individual IRB Chair(s) and members/alternate members have the knowledge, skills, and abilities appropriate to the respective roles and perform the responsibilities in an acceptable manner.

Geisinger policy requires that the IRB be constructed according to DHHS regulations (45 CFR 46.107) and FDA regulations (21 CFR 56.107). The IRB shall include at least five members, with varying backgrounds to promote complete and adequate review, including a nonscientific IRB member and an unaffiliated IRB member. A nonscientific IRB member may not have meaningful scientific or medical training or experience. Health professionals, regardless of discipline, may not be considered nonscientists. An unaffiliated IRB member must be an individual who is not otherwise affiliated with Geisinger and who is not part of the immediate family of a person who is affiliated with Geisinger. At least one nonscientist IRB member must always be present during a convened meeting to have a voting quorum. (See discussion of quorum in *Section 6.8- IRB Roster and Quorum Requirements*).

Appointment of IRB Members (Primary and Alternate), Length of Service, and Duties

IRB members (primary and alternate) are responsible for ensuring that the rights and welfare of research subjects are protected. Members vote to approve, require modifications in, disapprove, or defer research submitted to the IRB. Members' and alternate members' expectations are included with charge and any reappointment letter, which include regular attendance at IRB meetings, serving as reviewers for research within their areas of expertise, and serve as general reviewers on all research. Members may also be asked to participate in continuing member education and training.

IRB members (primary and alternate) are nominated from a variety of sources, including recommendations of IRB chair(s) members and staff, research, clinical, academic, operations, and administrative leadership. Consideration is given to ensure diversity within the IRB, including expertise, race, gender, and cultural backgrounds. A background knowledge of and current familiarity with affiliated institutional concerns helps ensure that the local research context is brought to IRB deliberations. Sensitivity to issues such as community attitudes is valued. The IRB includes consistent membership and involvement by at least one nurse to ensure this Magnet Program® requirement is met for Geisinger hospitals with Magnet® designation.

IRB members (primary and alternate) with expertise from various clinical disciplines are sought as needed. Annually, during evaluation of IRB members (primary and alternate), an active search for new nominees is conducted if gaps in membership are identified. Potential nominees are contacted by IRB leadership or Chair(s) to determine their interest and willingness to voluntarily serve on the IRB. When a nominee agrees to serve on the IRB, his or her resume` and any relevant documentation are reviewed and appointment decisions are made by the Director, Office of IRB and HRPP in collaboration with the IRB Chair(s) with input from the IO.
After a review of a potential IRB member's education, experience and other characteristics that might add diversity to the IRB, a new IRB member (primary and alternate) receives a formal appointment letter from the IRB Chair(s). IRB members (primary and alternate) serve an annual renewable term (from January 1 to December 31 but might vary depending upon need). At the end of the fiscal year, IRB members' (primary and alternate) contributions are evaluated by the IRB Chair(s) and Director, IRB Operations and HRPP and reviewed with the IO *(*see *Section 4- Knowledge of Human Research Protection Requirements*). If service is satisfactory, and continued membership is mutually desired, they are eligible for reappointment. All IRB members (primary and alternate) may be re-appointed at the end of their term without lapse in service.

Qualification to Perform Expedited Review

IRB Members' (primary and alternate) expectations are explained in appointment and reappointment letters, which include research training, conflict of interest disclosure, IRB meeting preparation, IRB meeting and member education attendance, serving as an IRB reviewer.
IRB members (primary and alternate) may perform protocol review according to the expedited procedure when the member has completed Geisinger-required research training and IRB member orientation, graduated from Geisinger IRB's Mentor/Mentee program, and indicated he/she is comfortable performing independent review.

The IRB Mentor/Mentee program includes the mentor and mentee working together to complete at least six reviews. Typically, the mentor is the assigned reviewer in iRIS for three reviews and the mentee works with the mentor to complete the reviews. Then if the mentee is comfortable, the mentee is the assigned reviewer in iRIS for three reviews, continuing to work through any questions with their mentor. After that, IRB staff work with the mentee to determine readiness to graduate from the program. If the mentee desires continued mentoring, that is done until the new member indicates they are comfortable independently reviewing IRB submissions.

Appointment of IRB Chair(s), Length of Service, and Duties

IRB Chair(s) work with IRB members, Director, IRB Operations and HRPP, institutional officials, and investigators to ensure that the rights and welfare of research participants are protected. In addition to the responsibilities of IRB membership, the Chair(s) conduct IRB meetings, work with staff to ensure effective and efficient operation of the IRB within all applicable regulatory requirements, serve as an expert resource for IRB members and staff and researchers/research staff, and participate as a member of Geisinger IRB Leadership Committee.
IRB Chair(s) can be nominated through many sources, including recommendations of previous IRB chair(s) members and staff, research, clinical, academic, operations, and administrative leadership. In addition to the characteristics sought in an IRB member (primary and alternate), these individuals possess demonstrated skills in leadership and group process and have IRB membership experience.

IRB Chair(s) are formally appointed/reappointed by the Institutional Official (IO). Chair(s) serve a three-year renewable term. IRB Chair(s)' contributions are evaluated annually by the Director, IRB Operations and HRPP with input from the IO *(See Section 4- Knowledge of Human Research Protection Requirements)*, and information learned from the evaluation is shared with the Chair(s) as the purpose of such evaluation is to recognize the Chair(s)' strengths, identify opportunities for improvement, and foster the Chair(s)' development. At the conclusion of the Chair(s)' term, if their service is satisfactory, and their continued service is mutually desired, they are eligible for reappointment.

Compensation of IRB Members

The IRB office supports IRB member participation in various ways. IRB Chair(s) departments receive a percentage of their salary to account for their time dedicated to IRB duties. IRB members' (primary and alternate) departments also receive salary recovery to account the time dedicated to IRB duties.

Geisinger Commonwealth School of Medicine employees, Geisinger IRB and Office of Research Compliance staff are not compensated for IRB service, as such activities are expectations of their positions.

An annual honorarium is provided to IRB members (primary and alternate) who are not Geisinger employees to acknowledge their IRB service.
As the budget permits, IRB members (primary and alternate) may also be eligible to receive a small award to support educational opportunities or certification as acknowledgement for their service on the IRB.

Alternate IRB Members

All IRB members, whether primary and alternate, are considered and treated similarly as IRB members, with the same requirements and expectations. Alternate members have similar qualifications and expertise as the primary IRB members for whom they may substitute and may represent similar interests or a specific vulnerable population. Alternate members are encouraged to attend all meetings, whether they are voting at particular meeting. They have access to the same agenda material as primary members to allow them to participate in IRB meeting deliberations and vote in place of their primary member when requested.

The IRB membership roster specifies which primary member each alternate member is qualified to replace. Terms of appointment, length of service, and duties are identical to that of primary IRB members. Alternate members must adhere to the same conflict of interest standards and documentation requirements as regular IRB members.

Ex Officio IRB Members

An ex officio member is designated as an IRB member by virtue of that individual's expertise or position in a particular field (e.g., bioethics, compliance). Ex officio members may participate in the IRB deliberations to provide information and expertise as requested by the IRB and are expected to adhere to the same conflict of interest standards and documentation requirements as primary and alternate IRB members. Ex officio members cannot vote on any IRB action or determination, and for this reason are sometimes

referred to as “non-voting” members. The IRB may accept ex officio members with the agreement of the IRB Chair(s) and the Director, IRB Operations and HRPP.

Liability Coverage for IRB members

Geisinger provides liability coverage under its insurance programs for IRB members acting in good faith in the performance of IRB duties. Geisinger’s Risk Management provides liability coverage of volunteer individuals, including community IRB members. All Geisinger-related physicians, staff, and students are covered in their capacity as employees and students.

Support of IRB Membership

The IRB has qualified staff, dedicated to supporting the IRB in its mission to protect human participants in research. The Director, IRB Operations and HRPP oversees the IRB staff and review resources at least annually to ensure there are sufficient resources to support IRB members. The IRB staff has knowledge, skills, and abilities appropriate to their respective roles.

For policies on qualifications, education, and periodic evaluation of ORC staff, see *Section 4- Knowledge of Human Research Protection Requirements.*

6.4 Scientific and Scholarly Expertise of IRB Members

Wide-ranging scientific and scholarly expertise among IRB members allows the IRB to review the broad variety of research in which Geisinger investigators are engaged. IRB members should be knowledgeable about relevant regulatory requirements and strive to remain impartial and objective during protocol review, deliberation, and voting. The IRB includes members who are particularly knowledgeable about research ethics and vulnerable research participants included in Geisinger research.

The IRB uses a “primary and secondary reviewer” system. IRB staff, in consultation with the IRB Chair(s) where appropriate, assign protocols to primary and secondary reviewers, based on each individual’s scientific, scholarly, professional, or clinical expertise. Primary and secondary reviewers must have the relevant expertise to conduct an in-depth review of the protocols to which they are assigned. If the IRB Staff cannot identify a primary and secondary reviewer with the appropriate scientific or scholarly expertise, the Director, Office of IRB and HRPP and IRB Chair(s) arrange for expert consultation and will not place the protocol on an IRB meeting agenda until appropriate consultation is conducted. Primary and secondary reviewers are expected to conduct an in-depth review, and it is the responsibility of primary and secondary reviewers to notify the IRB Chair or IRB staff should they feel unqualified or unable to do so. In such cases, the IRB staff will assign primary or secondary review responsibilities to another member who is appropriately qualified or obtain consultation from one or more experts outside the IRB (see Section 6.5, *Obtaining Additional Expertise/Consultation*).

When the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process includes one or more individuals who are knowledgeable about or experienced in working with these participants (e.g., children, pregnant women, adults unable to consent, students). The IRB staff reviews each study submission to determine whether it involves participants

vulnerable to coercion or undue influence and considers the participant population when assigning reviewers.

The IRB is constituted to possess and make use of collective knowledge of applicable regulatory and legal requirements; knowledge of professional standards and practices; knowledge of the local research context and research sites, and their capabilities and limitations; knowledge of community standards and attitudes; scientific, scholarly, clinical, and professional expertise; racial, ethnic, and cultural diversity; and representation of participants' perspectives.

6.5 Obtaining Additional Expertise/Consultation

When IRB Chair(s) or Director, Office of IRB and HRPP (in consultation with one another) believe IRB membership does not include the required expertise to review upcoming research or requires such assistance, the following occurs:

- The Director, Office of IRB and HRPP and/or the IRB Chair(s) invite individual(s) with competence in the specific areas to assist in evaluating the research and providing information pertinent to making an IRB determination.
- On an as-needed basis, an IRB primary and secondary reviewer may invite individuals with competence in special areas to assist in evaluating specific issues.

Reasons for seeking additional or special competence from outside experts may include (but are not limited to) the need for additional scientific, clinical, or scholarly expertise; the need for particular knowledge and understanding about potentially vulnerable populations of subjects; the desire to ensure appropriate consideration of race, gender, language, cultural background, and sensitivity to such issues as community attitudes.

After direction from the IRB Chair(s), IRB reviewers, or Director, IRB Operations and HRPP, the IRB staff contact the requested external consultant and provide him/her with all the protocol submission documents to allow them to conduct a thorough review.

When a consultant is used, the consultant must provide the IRB with a written report of his or her assessment which is uploaded in the study file within the iRIS and is available for review by IRB staff and members to permit protocol discussion at the convened IRB review and recorded in the IRB minutes.

All consultants, whether internal or external to Geisinger, must comply with the Geisinger **Guidance – IRB Members on Conflicting Interests**. They are not considered ad hoc IRB members and are not permitted to vote.

6.6 IRB Member, IRB Staff, and Consultant Conflicting Interest

*The IRB has and follows written policies and procedures so that members and consultants do not participate in the review of research protocols or plans in which they have a conflict of interest, except to provide information requested by the IRB. (**AAHRPPElementII.1.D**)*

Guidance – IRB Members on Conflicting Interests includes definitions of conflicting interest and outlines procedures for recusal. This policy applies to all IRB submissions and all IRB staff, members, and consultants.

The IRB triage procedures consider conflicts of interest when assigning submissions to IRB staff and members, such as when an individual is named in the research protocol or has a relationship with the research, sponsor, or any research personnel.

IRB members with a conflict of interest:

- Are excluded from participating in any review of a submission with which they have a potential conflict of interest.
- Are excluded from IRB submission presentation and discussion during an IRB meeting except to provide information requested by the IRB.
- Must leave the IRB meeting before submission presentation, discussion (except if requested by the IRB to provide information), and voting.
- Are excluded from voting and are not counted toward quorum for voting on the submission.
- IRB meeting minutes document when a member has a COI and leaves the meeting due to this conflict (including the time they left and what study number they are conflicted with)

See 45 CFR 46.107 and 21 CFR 56.107 for additional information.

IRB Member's Disclosure of a Conflicting Interest

All IRB members are required to complete an annual COI survey per **Geisinger Policy on Financial Conflicts of Interest in Research.** Members who realize they have a conflicting interest when they are assigned an IRB submission for review must notify the IRB staff or IRB Chair immediately so that the submission can be reassigned.

IRB chair(s), staff and members review the IRB meeting agenda within iRIS, which automatically identifies those members who are also study personnel related to the submission. This COI is indicated on the agenda within iRIS by a red "⊗" in the submission's COI column. Any conflicting interest for submissions on the IRB meeting agenda must be reported to the IRB Chair(s), Director, IRB Operations and HRPP, and/or IRB staff prior to the meeting whenever possible. If an IRB member realizes during a meeting that he/she may have a conflicting interest in a submission on the agenda, it should be immediately disclosed orally to the IRB Chair.

Consultant's Disclosure of a Conflicting Interest

The definition of conflicting interest as defined in the *Guidance - IRB Members on Conflicting Interests* extends to any consultant who may be asked to review a protocol. The IRB staff who contacts a consultant to inquire about review of a project is responsible for asking if the consultant has a conflicting interest in the project. If such an interest exists, then the protocol will not be assigned to the consultant.

A consultant with a conflicting interest can provide information to the IRB. If a consultant with a conflicting interest is the only appropriate resource for the IRB, (e.g., is the only scientist with sufficient technical understanding of the project) and if that consultant has been asked to provide information to

the IRB, then the conflict of interest must be disclosed to the IRB members reviewing the protocol or to the convened IRB during the meeting where the information is presented. Such a consultant is excluded from discussion except to provide information requested by the IRB, and if attending the meeting, must leave the meeting during discussion and voting.

IRB Staff and Conflicting Interest

IRB Staff must not participate in the review of any IRB submission in which they have a conflict of interest. IRB staff who realize they have a conflicting interest when they are assigned an IRB submission for review must immediately disclose the conflict and recuse themselves from participation in any review so that the protocol can be reassigned. Also, IRB Staff are required to complete an annual COI survey per *Geisinger Policy on Financial Conflicts of Interest in Research*.

Separating Competing Business Interests from Ethics Review Functions

*Geisinger has and follows written policies and procedures to separate competing business interests from ethics review functions. (**AAHRPP Element II.1.C**)*

Geisinger recognizes that officials who administer research programs, and individuals who are responsible for development activities (including raising funds) or business development, may represent competing business interests, or be in a position to influence programmatic and budgetary decisions and exert undue influence on the IRB or IRB member decisions. To avoid such influence on IRB determinations, individuals involved in these activities may not serve as IRB members and may not carry out the day-to-day operations of the review process unless there are compelling reasons to do so. Such reasons must be justified in writing, approved by the Chief Executive Officer (CEO) of Geisinger, and include specific measures to manage any conflict of interest or the possibility of undue influence.

As stated in Geisinger CEO's charge to the IRB, "…neither the CEO, IO, nor any other Geisinger official or committee may approve a protocol that has not been approved by the decision of the IRB, nor apply undue pressure on the Panel to reverse a decision (as further provided in Section 3)." See *Charge to the IRB Members on Human Subjects Research*.

6.7 Assessment and Evaluation of the IRB

*The IRB has qualified leadership (e.g., chair and vice chair) and qualified members and staff. Membership and composition of the IRB are periodically reviewed and adjusted as appropriate. (**AAHRPP Element II.1.B**)*

IRB composition and membership are evaluated at least annually by the Director, IRB Operations and HRPP and IRB Chair(s) with input from the IO. Membership is adjusted as needed to ensure appropriate knowledge of applicable regulatory and legal requirements; knowledge of professional standards and practices; knowledge of the local research context and research sites and their capabilities; knowledge of community standards and attitudes; scientific, scholarly, clinical, and professional expertise; racial, ethnic, and cultural diversity; and representation of participants' perspectives. Due to the increased complexity

of human research protocols submitted, the requirements regarding expertise often require the addition of new members. The composition of the IRB may change periodically as needed.
Education, training and periodic evaluation of IRB members, IRB Chair(s), and IRB staff are discussed in *Section 4.*

6.8 IRB Roster and Quorum Requirements

*The IRB membership permits appropriate representation at the meeting for the types of research under review, and this is reflected on the IRB roster. The IRB has: one or more unaffiliated members; one or more members who represent the general perspective of participants; one or more members who do not have scientific expertise; one or more members who have scientific or scholarly expertise; and, when the IRB regularly reviews research that involves vulnerable participants, one or more members who are knowledgeable about or experienced in working with such participants. (**AAHRPP Element II.1.A**)*

*The IRB has and follows written policies and procedures requiring research protocols or plans to be reviewed by individuals with appropriate scientific or scholarly expertise and other expertise or knowledge as required to review the research protocol or plan. (**AAHRPP Element II.1.E**)*

The process for appointing IRB members is described in HRPP Handbook Section 6.3 – IRB Composition and Membership, which includes thoughtful consideration of candidates to ensure Geisinger IRB has one or more unaffiliated members; one or more members who represent the general perspective of participants; one or more members who do not have scientific expertise; one or more members who have scientific or scholarly expertise; and one or more members who are knowledgeable about or experienced in working with vulnerable populations.

Geisinger IRB maintains the IRB Member roster within iRIS. Geisinger IRB roster is also maintained within its Office for Human Research Protections (OHRP) IRB Registration with required member information, including:

- Names of primary members
- Names of alternate members (and primary members for whom they substitute)
- Gender
- Earned degrees
- Scientific status
- Representative capacity
- Affiliation

IRB Co-Chairs have equal responsibility for function of the IRB. The Co-Chairs alternate chairing meetings and share responsibility for conducting IRB meetings and working with staff to ensure effective and efficient operation of the IRB within all applicable regulatory requirements. IRB Co-Chairs meet with the IRB staff the day before each meeting to review agenda items, discuss any questions or concerns, seeking to resolve them before the meeting if possible. The IRB Co-Chairs attend bi-monthly IRB Leadership Committee meetings where challenging matters related to human research are addressed. The IRB Co-Chairs share responsibilities when working with IRB members, Director, IRB Operations and HRPP, institutional officials, and investigators to ensure that the rights and welfare of research participants are protected.

Representative capacity is presented in enough detail to direct submission assignments to IRB members with appropriate expertise (e.g., children, pregnant women). When research protocols include vulnerable participants, who is knowledgeable about that population, or who has experience working with similar participants, should be present at the meeting.

Scientific status including the designation of "nonscientist" *(*see *Section 6.3- IRB Composition and Membership*), is determined during recruitment and annually upon evaluation of IRB members. Scientific status and area of scientific expertise (e.g., pediatrician, radiologist, psychologist, anthropologist, and pharmacist) are presented in sufficient detail to allow appropriate protocol assignment and in-depth protocol review.

Affiliation is determined during recruitment and annually upon evaluation of IRB members. An IRB member is considered affiliated if he or she, or any member of his or her immediate family, has any employment or other relationship (e.g., current employee, consultant, Board of Directors, current volunteer, trainee, or student) with **a** Geisinger entity.

Changes in IRB membership require submission of IRB Roster changes in Geisinger's IRB Registration at OHRP. The Director, IRB Operations and HRPP (or designee) submits IRB Roster revisions to OHRP per OHRP guidelines.

Quorum Requirements and Voting at IRB Meetings

*The IRB has and follows written policies and procedures for conducting meetings by the convened IRB. (**AAHRPP Element II.2.C**)*

Quorum is the minimum number and type of IRB members that must be present at a convened meeting. In order to review proposed research at a convened meeting, a majority of the primary members of the IRB must be present, including at least one member whose primary concerns are in nonscientific areas (45 CFR 46.108(b); 21 CFR 56.108(c)). If a majority of the IRB primary members is not present, or if a nonscientist is not present, then quorum has not been met.

The IRB Chair(s) are voting members of the IRB. The Chair chairing the meeting, with the assistance of IRB staff, determines that quorum has been established and maintained, chairs the meeting discussions, and calls for votes as appropriate. The IRB Chair chairing the meeting will be considered "voting" and will count toward quorum unless he/she has a conflict with the submission under review.

Maintenance of quorum and voting at convened meetings is based on the following standards:

- Quorum must be maintained to permit voting during an IRB meeting.
- Quorum is a majority (one more than 50%) of the number of primary IRB members, including at least one member whose primary concern is in non-scientific areas.
- A non-scientist must be present to conduct a convened meeting.
- Primary members or the member's alternate will be designated as "voting" at each IRB meeting.
- IRB staff will announce members designated as "voting" at the beginning of each IRB meeting and will announce any changes to designated voters throughout the meeting.

- For research to be approved, the submission must receive the *approval of a majority* of voting members present at the meeting.

IRB meetings are conducted via MS Teams business communication platform and may include in-person attendance when permitted by the institution. All IRB members have access to all meeting materials via iRIS access, including IRB meeting agenda, minutes, and submission documents. All members present, regardless of voting status during the meeting, have opportunity to participate actively and equally in all IRB deliberations.

IRB meeting voting procedures include the following:

- IRB members vote verbally, responding to the meeting chair's call for votes as follows: 1) approve, 2) oppose, or 3) abstain.
- Member(s) leaving the meeting due to a conflicting interest, or for any other reason, will not be recorded as part of the quorum for a particular vote.
- An individual who is not listed on the official IRB membership roster may not vote with the IRB.

A non-voting ex-officio IRB member cannot vote with the IRB.

Ad hoc consultants cannot vote with the IRB.

A non-scientist IRB member must be present throughout the IRB meeting in order to conduct IRB business and vote.

- Regular attendance of unaffiliated members is expected. Unaffiliated members represent the general perspective of participants and should be actively engaged and participate in IRB meetings.
- Individual IRB members may satisfy more than one required type of member (e.g., a non-scientific member may also be the unaffiliated member).
- When a primary member and his/her alternate both attend a meeting, either person (but not both) may vote on each protocol. IRB staff will announce the person designated as "voter."

Voting by proxy is not permitted.
If the quorum is not maintained during a meeting, RB members being present or an absence of a nonscientist member, the IRB cannot take any further actions or vote until the quorum is restored.

- *IRB* staff is responsible for monitoring the members present at a convened IRB meeting to ensure that at the beginning of the meeting and for each subsequent vote the meeting is appropriately convened.
- When the IRB reviews research that involves participants vulnerable to coercion or undue influence, at least one member must be present who is knowledgeable about or experienced in working with these types of vulnerable populations.
- Geisinger IRB is not constituted to review studies planning to enroll Prisoners per 45 CFR 46 (Subpart C).

IRB minutes shall include documentation of quorum and votes for each IRB action and determination by recording votes as follows:

- Total number voting
- Number for

- Number opposed
- Number abstaining
- Names of those recusing

See *Section 8.3 – IRB Minutes* for additional information about convened meeting minutes.

6.9 Meeting Times and Materials

*The IRB has and follows written policies and procedures for conducting meetings by the convened IRB. (**AAHRPP***

Convened IRB meetings are held twice a month according to a published schedule, typically the first and third Thursday of each month.

Individual meetings may be rescheduled, or additional meetings may be held, as needed by agreement of the IRB Chair(s) and the Director, IRB Operations and HRPP.

The deadline for receipt of IRB submissions for review at convened meetings is posted on the published meeting schedule, and the deadline is typically three weeks prior to the meeting.

Submissions are included on the meeting agenda after pre-review is complete, and IRB staff determine that the submission is ready for review at the convened IRB meeting.

Review and Preparation Time

Protocol Materials

Protocol materials are received approximately three weeks prior to a meeting to allow IRB staff sufficient time to review the submission for completeness and allow questions to be resolved with the study team prior to the convened meeting.
Review assignments are done via iRIS, which makes available all necessary protocol materials to all members and reviewers.

For protocol materials provided to members, see *Sections 7.5 - Assignment of protocols to IRB members* and *7.7- Protocols Presented at a Convened Meeting.*

Meeting Documents

Protocol materials are available online, via the web-based “iRIS” system. All IRB Members in attendance at a convened meeting have access to all pertinent meeting material, which is also projected at the meeting.

Approximately seven days prior to the IRB convened meeting, all members are notified electronically that the agenda material is ready for review. This includes:

- Agenda List for the coming meeting, typically containing:
  - a statement on confidentiality of meetings,

    - vote on previous meeting minutes,
    - education and information items (including reports to be discussed)
- Minutes from the previous meeting.

Meeting Agenda details**:**

- All submissions that will be presented and voted upon during the meeting,
- All submissions (new, minor modifications, or continuing reviews) that, since the previous convened meeting for this IRB, have been reviewed by the expedited or exempt process and recommended for approval, and do not need to be presented at a convened meeting,
- Other items (such as findings on Reports which have not required presentation at the convened meeting).

Section 7 - Systematic Review

7.1 Protocol Review

*The IRB has and follows written policies and procedures to conduct reviews by the convened IRB: (**AAHRPP Element II.2.D**)*

- ***Element II.2.D.1**.–Initial review*
- ***Element II.2.D.2**.–Continuing review*
- ***Element II.2.D.3**.–Review of proposed modifications to previously approved research*

*The IRB has and follows written policies and procedures to conduct reviews by an expedited procedure, if such procedure is used. (**AAHRPP Element II.2.E**)*

- ***Element II.2.E.1**. – Initial review*
- ***Element II.2.E.2**. – Continuing review*
- ***Element II.2.E.3**.–Review of proposed modifications to previously approved research*

All new Geisinger human research (as defined in Section 1.3- Delegation of Responsibility for Geisinger HRPP Implementation) and modifications to approved research (except when the modification is necessary to eliminate apparent immediate hazards to participants) must be prospectively reviewed by the IRB. In addition, no previously approved human subjects research may be continued beyond the approval expiration date without prospective approval (continuing review).

7.2 IRB Study Application

Geisinger IRB submissions are via the web-based "iRIS" system, and include the following submission forms:

- Study Application
- Exempt Study Application
- Application for Request for Ceding to an External IRB
- Emergency Use Notification Application
- Research Determination Worksheet Study Application
- Amendment/Modification Form
- Key Study Personnel Amendment/Modification Form
- Continuing Review Report Form
- Final Report Form
- Prompt Report Form – (Reports of non-compliance, unanticipated problems and events and information requiring prompt reporting to the IRB)

Attempts have been made to avoid duplication of details within the study application and in the formal protocol attached to the study application during the submission. The study application is typical of most electronic applications and directs investigators to respond to questions applicable to the study submission. The study application is comprised of many sections, such as:

- study title

- study personnel
- study location
- funding
- resources
- collaboration/multi-site, participant population
- lay summary
- drugs (investigational and commercial)
- devices (non-significant risk and significant risk)
- recruitment methods and screening procedures
- inclusion and exclusion criteria
- inclusion of vulnerable populations
- potential risks and benefits
- procedures to protect privacy and maintain confidentiality of data
- conflict of interest
- consent and assent and HIPAA authorization

A "validation process" feature within iRIS requires that each question applicable to the study is answered before submission to the IRB is permitted. The investigator will receive an error message stating that a section was not completed.

Protocol Review Types (Exempt, Expedited or Convened)

Exempt:
Geisinger requires protocols qualifying for exemption from applicable federal, state and local regulations to be submitted for IRB review and confirmation that criteria for exemption are met and Geisinger policies are followed. See Guidance – Exempt Review Categories. All protocols submitted for exemption review must meet the requirements set forth in 45 CFR 46.104. Geisinger is not applying Exemptions 7 and 8 related to Broad Consent at this time.

Limited Review:
Review by an IRB member to ensure provisions are adequate to protect the privacy of research participants and confidentiality of data as a condition for Exemption 2(iii) and 3(i)(C) categories set forth in 45 CFR 46.104. Geisinger is not applying Exemptions 7 and 8 related to Broad Consent at this time.

Expedited Review:
Protocols submitted for expedited review must meet the requirements set forth in 45 CFR 46.110 (the research involves no more than minimal risk and falls within the categories published in the November 9, 1998, Federal Register 63 FR 60364-60367 and 63 FR60353-60356 DHHS-FDA lists of research eligible for expedited IRB review).

Convened Review:
All protocols that do not qualify for exempt or expedited review are subject to review at a convened IRB meeting.

7.3 Submission, Preliminary Review and Assignment to IRBs

Submission, Triage, and Pre-Review - New Protocols
New protocols are submitted and received directly within the iRIS electronic IRB system. IRB staff triage all submissions. If submission appears complete (e.g., ensure research training and COI disclosure is complete and current) during the triage, the submissions are assigned to IRB staff to perform a pre-review of the submission. The pre-review includes review for protocol completeness and confirms the protocol review type (Exempt, Expedited, or Convened) type selected by the PI as appropriate for the study.

Assignment to IRB - New Protocols
Once a new protocol submission is deemed complete, the protocol is assigned for review. To avoid any potential conflicting interest, new protocols are not assigned to an IRB member who is also an investigator or part of the study team on the research project. After taking into consideration any conflicting interest issues, assignment of protocols to the IRB reviewer is based on reviewer expertise and capacity, study type and population, protocol review type, the order (by date) the protocol was submitted to the IRB, and for protocols subject to convened review with assignment to the next IRB meeting.

Assignment to IRB: Amendment/Modification; Continuing Review Report; Unanticipated Problems; Non-Compliance and Final Reports:
When possible, subsequent submissions for approved protocols are pre-reviewed and assigned to the IRB Member reviewer who initially reviewed the protocol. After taking into consideration any conflicting interest issues, assignment of submissions to the IRB reviewer is based on reviewer expertise and capacity, study type and population, protocol review type, the order (by date) the protocol was submitted to the IRB, and for protocols subject to convened review with assignment to the next IRB meeting.

- Protocol Review Material and Information

Protocol submission forms in iRIS include the following:

- Study Application
- Exempt Study Application
- Application for Request for Ceding to an External IRB
- Emergency Use Notification Application
- Amendment/Modification Form
- Key Study Personnel Amendment/Modification Form
- Continuing Review Report Form
- Final Report Form
- Prompt Report Form

All IRB members, reviewers, and staff have full access to all protocol information and materials upon complete submission to the IRB. All new submissions include the iRIS study application. The study application may need to be amended with an Amendment/Modification Form if details outlined in the application change. Protocols must be submitted for all studies, except those that meet Exemption criteria. The Exempt Study Application captures information required to make an exempt determination and assess institutional research requirements.

In addition, all IRB staff and members have access to all documents submitted in support of the study submission to conduct a thorough review. This may include any or all the following as applicable to the submission:

- Informed consent and assent documents
- Phone scripts
- E-mail text
- Recruitment materials, including advertisements, letters, MyChart messaging
- Questionnaires and surveys
- Supporting protocol (if applicable, sponsor or DHHS-approved protocol if DHHS funded)
- If applicable, the sponsor's informed consent document (including DHHS-approved sample consent document, when one exists)
- Investigator's brochure (investigational drugs)
- Device manual or report of prior investigations (devices)
- FDA letter, if applicable
- Relevant external grant, if required by sponsor
- All relevant reports, including multi-center trial reports (at continuing review)
- Curriculum Vitae or Bio sketch for all study team members
- IBC approval, if applicable
- RSC approval, if applicable
- Signed billing determination, if applicable
- SCP (Security, Compliance, Privacy) Risk Assessment/approval (when disclosing PHI outside of the covered entity)

Additional information may be requested to complete review of a protocol.

7.4 Assignment of Protocols to IRB Members

*The IRB has and follows written policies and procedures requiring research protocols or plans to be reviewed by individuals with appropriate scientific or scholarly expertise and other expertise or knowledge as required to review the research protocol or plan. (**AAHRPP Element II.1.E**)*

Reviewer assignments are made with the objective of matching reviewer expertise and experience with protocol subject matter and population(s) included in the research. (See Section 6- Structure and Composition of the IRB). For approved protocols, an attempt is made to assign subsequent submissions to a member who was an assigned reviewer when the study was first approved.

"Nonscientific" members assigned to review protocols are valued for the patient and community perspective they bring to the process of ensuring the protection of research participants.

Convened Review

The IRB ensures IRB approval criteria are met when reviewing all research submissions, including continuing review, and review of a modification to previously approved research when the modification affects a criterion for approval. (HHS – 45 CFR 46.111 and FDA – 21 CFR 56.111)

New Protocols:
The IRB utilizes a primary reviewer and secondary reviewer system for protocols subject to convened review. New protocols are assigned by the IRB staff to a primary reviewer and secondary reviewer to present the protocol at the convened meeting. Both reviewers review the complete submission. The primary reviewer conducts an in-depth scientific review of the protocol and the secondary reviewer is focused on the consent form and other materials provided to study subjects. All members have access to all study documents within the iRIS electronic IRB System and are expected to review all study submission materials in preparation for convened meeting deliberations. All reviewers receive an automated notification of the reviewer assignment within the electronic IRB system. All IRB members can view upcoming meeting agendas within iRIS at any time, and they receive the upcoming meeting agenda via email several days before the meeting.

If IRB staff identifies or is informed by the assigned reviewer, IRB chair, or other member or alternate that there is not an appropriate primary reviewer with scientific or scholarly expertise, or other expertise or knowledge, to conduct an in-depth review of the protocol, the submission is deferred to another IRB meeting to the allow the opportunity to obtain the appropriate outside consultation and review. The Director, IRB Operations and HRPP, assigned IRB reviewers, and/or IRB Chair(s) upon preliminary review of the submission can determine whether a consultant is needed. The process by which consultation is accomplished is described in Section 6.5.

Major (or “Substantive”) Amendment/Modifications:
The following amendment/modifications are subject to convened review and if possible are assigned by the IRB staff to the original reviewer of the protocol or another IRB member with relevant knowledge and/or expertise. The reviewer reviews and presents the protocol at the convened meeting.

A major (substantive) modification is one which potentially increases risks to participants, directly relevant to required IRB determinations, or is a greater than minor change to any of the following:

- Consent form
- Research design or methodology
- Subject population enrolled in the research
- Qualifications of the research team
- Facilities available to support safe conduct of the research
- Any other factor which would warrant review of the proposed changes by the convened IRB

Continuing Review:
For all protocols initially subject to convened review, the continuing review submission undergoes convened review, unless it meets the criteria for expedited review (see below). Those which will undergo convened review are assigned by the IRB staff to the original reviewer of the protocol if possible or to a reviewer with relevant knowledge and/or expertise. The reviewer reviews and presents the protocol at the convened meeting.

Prompt Reports (Unanticipated Problems and events and information requiring prompt reporting):
See Section 3.8 – Prompt Reporting for Reportable Events.

Expedited Review

*The IRB has and follows written policies and procedures to conduct reviews by an expedited procedure if such procedure is used. (**AAHRPP Element II.2.E.**)*

See OHRP guidance, Expedited Review Categories.

All submission material is processed through the iRIS electronic IRB system; therefore, all IRB members, including any assigned reviewers, have access to all submission material and documents to conduct a thorough review of the submission. Assigned expedited reviewers must thoroughly review all submission documents and materials to complete the assigned review.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers. In reviewing the research, the reviewers may exercise all the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in 45 CFR 46.108(b).

Expedited reviews are assigned by the IRB staff to an IRB member qualified to conduct expedited review. (See Section 6- Structure and Composition of the IRB for reviewer qualifications.)

The assigned reviewer ensures IRB approval criteria are met when reviewing all research submissions, including continuing review, and review of a modification to previously approved research when the modification affects a criterion for approval. (HHS – 45 CFR 46.111 and FDA – 21 CFR 56.111)

The evaluation by the assigned reviewer determines whether research undergoing initial review, continuing review, or review of modifications using the expedited procedure meets all the applicability criteria and represents one or more of the approvable categories of research.

New Protocols (Initial Review Submission Form)
Protocols subject to expedited review follow a single reviewer process and are assigned by the IRB staff to a qualified IRB member.

Amendment/Modifications (Minor) (Amendment/Modification Form)
A minor modification eligible for expedited review is one in which all the following are true in the judgment of the IRB reviewer:

1. Any increment in risk is less than minimal risk.
2. All additional activities or procedures would have been eligible for expedited review had they been part of the initial protocol review.
3. Either the research is minimal risk or the proposed changes do not alter the study design.
4. Modification/changes that do not affect the study approval criteria.

If the modification changes the review type appropriate for the study, the IRB staff will convert the protocol to the appropriate review type. The IRB reviewer makes the final determination of whether changes to the protocol are “major” or “minor.”

Continuing Review (Protocols subject to convened review initially) (Continuing Review Report Form)
For a protocol initially subject to convened review, the continuing review submission undergoes expedited review:
If (category 8):

a) The research is permanently closed to enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long term follow-up of subjects; or
b) No subjects have been enrolled and no additional risks have been identified; or
c) The remaining research activities are limited to data analysis,

If (category 9):

a) For continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Continuing Review (Protocols subject to expedited review initially) (Continuing Review Report Form)
For a protocol initially subject to expedited review, the continuing review submission undergoes expedited review if:

- It does not include any modifications, or
- If modifications are included, the proposed modifications would have been eligible for expedited review had they been part of the initial protocol.

For continuing review of research, all IRB members, including the assigned reviewer have access to the entire protocol submission within the iRIS electronic IRB system, which includes the complete protocol, including any protocol modifications previously approved by the IRB. Protocols subject to expedited continuing review are assigned to an IRB member reviewer (preferably the original reviewer of the protocol) and are not presented at a convened meeting; however, the completed reviews are reported on the IRB agenda and available for IRB members to view.

The continuing review report includes a status report on the progress of the research, which includes:

- A summary since the last IRB review of:
    - Current enrollment status
    - Status of participant interaction and study activity
    - Serious Adverse events, untoward events, and adverse outcomes experienced by participants
    - Unanticipated problems involving risks to participants or others
    - Participant complaints
    - Protocol deviations and/or non-compliance
    - Amendments or modifications
    - Any relevant recent literature
    - Any interim findings
    - Any relevant multi-center trial reports

Removal of Continuing Review Requirement (as permitted in 2018 Revised Common Rule)

Effective May 1, 2018, GIRB applied flexible provisions adapted from the Final Revised Common Rule 45 CFR 46 Subpart A - Basic HHS policy of Protection of Human Research Subjects (January 18, 2017) to research that was neither federally-sponsored nor FDA-regulated. As such, GIRB eliminated the continuing review requirement for most minimal risk research and required documentation of rationale for continuing review of research that otherwise would not require continuing review.

New studies determined to be minimal risk and approved on or after January 21, 2019 (and ongoing studies that did not already transition prior to this date) are evaluated to assess criteria to remove the requirement for continuing review at the time of the study approval or continuing review occurring on or after January 21, 2019. The determination is based on investigator responses to questions related to sponsor or regulated status (e.g., studies subject to FDA regulations must undergo continuing review regardless of risk level), status of participant interaction and research activities and the criteria outlined below. Continuing review requirements are communicated to the study PI in the Review Outcome Letter and documented in the study's electronic IRB record, and Continuing Review and Expiration dates are removed from the Study Outcome tab and Outcome letter when the IRB reviewer determines continuing review is not required.
If the IRB determines continuing review is required for research that otherwise would not require continuing review as described below, the rationale for conducting continuing review of research will be documented in the IRB records and communicated to the investigator.

Removal of the requirement for continuing review does not impact other IRB submission requirements, e.g., any modifications to the IRB-approved protocol, documents, study personnel, etc. must be submitted for IRB approval prior to implementation of the change. In addition, this does not remove the requirement for reporting to the IRB any Unanticipated Problems (UPs) that increase risk to participants or non-compliance that meet criteria for Prompt Reporting.

Ongoing continuing review of research is not required in the following circumstances:

- Research meets the definition of minimal risk, as defined in 45 CFR 46.102 unless the research is subject to FDA regulations

Research is eligible for expedite review in accordance with 45 CFR 46.110 with the following exceptions (per OHRP 2018 Requirements FAQs). Research that meets criteria for either:

- Expedited category 8(b) - no subjects have been enrolled and no additional risks have been identified. (Continuing review may be valuable because research within this category may involve interactions, interventions, or procedures that might present more than minimal risk to subjects. Continuing review provides the opportunity to monitor these studies once recruitment begins.)
- Expedited category 9 - (i) the research is not being conducted under an investigational new drug application or investigational device exemption, (ii) categories two (2) through eight (8) of the OHRP Expedited Review Categories (1998) do not apply, and (iii) the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified. (Continuing review of studies that qualify for expedited category 9 provides the IRB with the opportunity to evaluate the progress of ongoing research activities otherwise not included in the list of permissible expedited review categories.)

- Research was reviewed by the IRB in accordance with limited review required for certain exemption determinations

- Research has progressed to the point that it only involves one or both of the following:
  - Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
  - Collecting data from routine care activities that participants would undergo regardless of study participation, typically as long term follow up.
- Additional criteria:
  - FDA regulations do not apply to the study
  - Study sponsor does not require continuing review
  - The study does not involve additional regulatory oversight (e.g., conflict of interest (COI) management plan
  - There are no restrictions imposed by GIRB on the PI
  - The study or PI do not have a pattern of serious or continuing research non-compliance

Final Reports

Final Reports are subject to administrative review, are assigned to an IRB Staff member, and are not presented at a convened meeting; however, the reviews are reported on the IRB agenda and available for IRB members to view.

7.5 Protocol Review – Pre-Review

General Process for All Protocol Submissions

The IRB utilizes a pre-review process, which involves preliminary review by IRB staff followed by a thorough review by IRB member reviewer(s). While not always possible, submissions assigned to a convened meeting should be fully reviewed by the assigned reviewer(s) prior to the meeting date. Reviewer questions and/or recommendations may then be communicated to the investigator/study team and facilitate response for consideration before or during the convened IRB meeting.

During the submission pre-review and review process, IRB staff and reviewer(s) enter comments, questions, or recommended modifications to the study application, protocol or associated documents (e.g., consent forms, advertisements, protocol, etc.) into the iRIS Reviewer Sheet and/or iRIS stipulations/recommendations section for the submission.

7.6 Protocols Presented at a Convened Meeting

*The IRB has and follows written policies and procedures for conducting meetings by the convened IRB. (**AAHRPP Element II.2.C**)*

Quorum

An IRB quorum consists of one more than half of the number of primary members and includes a member whose training, background, and occupation would incline them to review scientific activities from the standpoint of someone within a behavioral or biomedical research discipline as a scientist, and a member whose training, background, and occupation would incline them to view research

activities from a standpoint outside of any biomedical or behavioral scientific discipline as a non-scientist. Expert reviewers/consultants are not required to attend the convened meeting; however, they must provide a written overview of the study to the IRB. There may be times when the IRB Chair(s) and/or Director, IRB Operations and HRPP invite them to attend the IRB meeting; however, they cannot vote.

A quorum, which includes both a scientific and non-scientific IRB member, must be maintained throughout the IRB meeting deliberations and voting. No IRB actions can take place without such a quorum. This is monitored by designated IRB staff during the meeting, and any changes in quorum are announced to the chair so decisions about the ability to proceed can be made.

Materials Available at Convened Meetings

Prior to the convened meeting, all IRB members are notified electronically that the upcoming meeting agenda and all meeting materials are available for members' review in preparation for meeting discussion and voting. In addition to the submissions to be reviewed during the upcoming IRB meeting, the agenda includes:

- previous meeting minutes for review and vote;
- any educational and informational items to be presented during the meeting; and
- list of submission reviews completed between finalization of the last meeting agenda and finalization of the current meeting agenda for IRB member information and opportunity to review if the would like.

Electronic access enables assigned reviewers and all IRB members to see all the details of the current study submissions and related submission components to be reviewed and voted upon at the meeting (e.g., study application, protocol, informed consent, forms), assigned reviewer assessment and comments and any associated submission report forms (e.g. modification, continuing review, reportable events). For research that is already approved, all IRB members have access to previous submissions and previously approved documents. Reviewers are expected to review the information sufficiently to provide comments (if any) before the meeting and present their review to the convened IRB during the meeting. All materials submitted supporting a protocol are available to voting members during the meeting.

Meeting Deliberations

The primary and secondary reviewers are considered the lead reviewers on the IRB for submissions assigned to them for review. They are responsible for:

- Being thoroughly versed in all details of the research,
- Conducting an in-depth review of the research using the IRB Reviewer Sheets and tools as guidance.
- Documenting their reviewer assessments and recommendations within the iRIS Reviewer Sheet
- Presenting submission details, their assessment and recommendations to the convened IRB

The primary and secondary reviewers are designated as the presenters who present the study submission for discussion at the convened meeting. All IRB members have an opportunity to participate in discussion of each submission during the convened IRB meeting. The members and

reviewers consider the approval criteria set forth in 45 CFR 46 and/or 21 CFR 50 (for FDA-regulated research) in reviewing a protocol submission. The IRB confirms the proposed study submission and submission components (e.g., protocol, informed consent documents, recruitment documents) are accurate and complete.

Controverted issues that have not been resolved during the review prior to the convened IRB meeting are discussed. Once discussion is complete, the meeting chair calls for a motion, any questions and vote by IRB members designated and announced as "voting members" during the meeting.

Range of Actions on Protocol Review at Convened Meetings

The convened IRB must systematically evaluate each protocol submission to ensure the protection of research participants and determine whether the protocol submission meets applicable HHS or FDA approval criteria (HHS – 45 CFR 46.111 and FDA – 21 CFR 56.111).

Review Actions

Regardless of the submission type (e.g., initial review, continuing review, amendment/modification review), the possible decisions by vote of a majority of the convened IRB (quorum) include the following review actions:

- **Approve with no changes:**
  - Approved by the convened IRB. The research may proceed.
  - Approval requires an affirmative vote by a majority of the convened quorum.
  - If an amendment or continuing review is submitted on a more than minimal risk study which was previously reviewed and approved via convened review and the protocol has been modified to the extent that it now qualifies for expedited review, the IRB can change the protocol review designation from convened to expedited review.
- **Contingent/Minor Modifications:**
  - The convened IRB determined that the submission was approved contingent upon the investigator making minor changes (simple concurrence) to the submission.
  - The minor changes, stipulations, etc., are clearly outlined by IRB members at the convened meeting and the IRB outcome letter indicates that approval is contingent on the PI accepting the IRB stipulations or making any required changes to documents requested by the IRB.
  - The research may not proceed until an IRB approval letter is sent to the PI after the IRB staff (in consultation with the IRB reviewer, chairperson, or any other designated individual(s) if required by the IRB) has reviewed and accepted as satisfactory all submitted investigator responses required by the IRB. This review is carried out via an administrative review process.
- **Deferred (Tabled)/Major Modifications:**
  - The convened IRB determined that submission may be approvable but requires greater than minor (substantive) changes or requirements, requests for more information for IRB consideration, and other issues related to the criteria for approval that require re-submission, review and approval by the convened IRB to meet the approval criteria.

- The major changes, stipulations, etc., are clearly outlined by IRB members at the convened meeting and the IRB outcome letter indicates that approval is contingent review and approval of the investigator's Submission Response by the convened IRB.
- The research may proceed only after the convened IRB has reviewed and approved the Submission Response with required changes to the research, and the investigator receives an IRB approval letter.
- A protocol will be deferred until it is approved (or eventually disapproved) by the voting members at a convened meeting.
- If the primary and secondary reviewers are not available at subsequent meetings where a deferred protocol is reviewed, additional reviewers will be assigned to review and present the protocol for re-review.

- **Disapproved:**
  - The convened IRB has determined that the research cannot be conducted at Geisinger or under the auspices of Geisinger (e.g., IRB approval criteria, regulatory requirements, Geisinger HRPP standards, or other stipulations have not been satisfied).
  - The investigator and study contact are notified via IRB outcome letter that the protocol was not approved by the IRB, explaining the reason(s) it was not approved, and giving the investigator an opportunity to respond or appeal the IRB decision in person or in writing. (The details and process for such an appeal are set forth in Section 6 of the HRPP Handbook.)

IRB meeting minutes document the deliberations, actions, and votes for each protocol submission undergoing Convened Review.

IRB Approval Date and Determination of Expiration Date

The approval date for a protocol subject to either initial or continuing convened review is the date of the IRB meeting at which the protocol was approved. The IRB can approve a protocol for a maximum of 364 days (12 months) from the date of approval but may approve for a shorter period. Approval of a protocol modification does not alter the expiration date. The expiration date of a study approved for 12 months is the last day the protocol is approved (e.g., protocol approved on January 1, 2014 will expire at midnight on December 31, 2014).

Examples for a shorter approval period would include:

- The IRB may approve a study for 1, 2, 3, or 6 months or may stipulate the approval on further IRB review after a defined number of participants have been enrolled (e.g., review after the first three subjects receive a Phase I drug that has never been tested in humans).
- If any of the following are true, the IRB may perform review more often than annually: (a) novel high-risk study using new therapeutic modality; (b) phase I studies of a new drug or biologic that has never been tested in humans; (c) studies involving a novel, significant-risk medical device that has never been tested in humans; (d) more than minimal risk, investigator-initiated studies with very little preliminary data; and (e) other high-risk studies as IRB members deem appropriate (this includes research for which the IRB determines that reports to the IRB of monitoring data should be more frequent than annually).

Approval contingent on minor conditions:

- The protocol initial approval date is recorded as the date on which the convened IRB approved the study contingent on minor conditions being addressed. However, the "effective" date of initial approval is the date on which the IRB member reviewer, chairperson (or designee) has reviewed and accepted as satisfactory any documents or any other responsive materials required by the IRB.
- The approval letter is not sent until all stipulations/contingencies have been met.
- No research study activities involving human subjects may be initiated until the conditions have been satisfied in the manner set forth by the IRB and the approval becomes effective.
- The expiration date is determined in reference to the date the study was approved by the convened IRB, contingent on minor conditions being addressed. For example:
  - 12/1/14 – convened IRB review date requiring minor modifications
  - 1/1/15 – administrative review with approval acknowledging all changes were made
  - IRB approval date is 1/1/15 and study expiration date is 11/30/15

Approval contingent on substantive changes or requirements, requests for more information for IRB consideration, or other issues related to the criteria for approval that require review and approval by the convened IRB:

- The protocol initial approval date is recorded as the date on which the convened IRB approved the study after conditions were addressed and approved. The approval date is the date on which the convened IRB reviewed and accepted the responses by the PI and all stipulations/contingencies were met.
- The approval letter is not sent until all stipulations/contingencies have been met.
- No research study activities involving human subjects may be initiated until the conditions have been satisfied in the manner set forth by the IRB and the approval becomes effective.
- The expiration date is determined in reference to the date the study was approved by the convened IRB. For example:
  - 12/1/14 – convened review date where modifications/stipulations/contingencies were accepted
  - IRB approval date is 12/1/14 and study expiration date 11/30/15

If during continuing review the study expires before the conditions have been reviewed and approved at the convened IRB meeting, all research activities must stop until approval is obtained.

Research that continues after the approval period expires is considered research conducted without IRB approval. If investigators fail to receive continuing review approval prior to the study expiration date, the PI is notified that the study expired and that research activities -- including but not limited to recruitment, advertisement, enrollment, interventions, interactions, data collection, and data analysis -- are unapproved and must stop, unless the IRB determines that continued involvement is in the best interest of enrolled subjects who are still receiving study-related interventions. In this case of risk of harm to participants from halted research activities, the PI must notify the IRB and immediately submit a list of participants for whom stopping research activities would cause harm. The IRB will determine whether the continued involvement is in the best interests of the individual participant(s).

Section 8 - Documentation of IRB Activities

8.1 IRB Protocol Files

*The IRB maintains a complete set of materials relevant to the review of the research protocol or plan for a period sufficient to comply with legal and regulatory requirements, Sponsor requirements, and organizational policies and procedures. (**AAHRPP Element II.5.A**)*

The IRB staff maintains documentation of activities. IRB records include IRB protocol files, minutes for convened IRB meetings, and other documentation.

The IRB utilizes an electronic, web-based IRB system ("iRIS") to receive, process and maintain study submission documents and correspondence with investigators/study teams related to study submissions. All study-related documents are accessible by investigators and study team members and IRB staff and members.

Electronic Database, Submission, and Review System (iRIS)

The iRIS electronic IRB system maintains electronic records of *all* submission documents submitted for every protocol event (new study submission, amendment/modification, continuing review, prompt report, and final report). The iRIS electronic IRB system contains a search function for locating and retrieving protocols by IRB number, protocol title, name of Principal Investigator (PI), names of any co/sub-investigators and study personnel, review type, meeting date, sponsor, reviewer, study application questions, combinations of the above categories and more. Electronic copies of all submission materials and IRB correspondence, which includes IRB review and outcome, can be accessed through iRIS on an event-by-event basis through the iRIS Submission History function, thus all documents supporting each protocol event are accessible to reconstruct the entire history of a protocol.

An iRIS study file for human subjects' research for which Geisinger IRB is the reviewing IRB contains the following, as applicable to the research:

- **Study Application** - Submitted for all human subjects' research.
- **Protocol** – Submitted for all non-exempt human subjects' research, whether investigator-or sponsor-written protocol.
- **Bio-sketch or Curriculum Vitae** – Submitted for all iRIS users within the individual's User Profile upon account creation and accessible within the study's "Study Management" tab.
- **Amendment/Modification Form** - Submitted for modifications to already approved research.
- **Key Study Personnel Amendment Form** – Submitted for modifications to study personnel.
- **Continuing Review Report Form** - Submitted for continuing review of research.
- **Prompt Report Form** - Submitted for reportable events, including unanticipated problems and non-compliance.
- **Final Report Form -** Submitted for closing protocols.
- **Significant new findings –** Submitted via Amendment/Modification Form or Prompt Report Form.

- **Informed consent, assent, parental permission, and HIPAA authorization -** The protocol file includes all versions of these forms as applicable to the study, including the currently approved form(s). When sponsor versions of the form(s) should also be included in the protocol file.
- **Scientific evaluations of the proposed research** - Documentation of scientific review by Geisinger Scientific Review Committee (SRC) or an external scientific peer review. (See *Section 1.7- Scientific and Scholarly Validity Review and Ethics Review* for information on scientific and scholarly review.)
- **Sponsor Materials –** Sponsor materials related to the study or investigational product (e.g., Investigator's Brochure, device use instructions).
- **FDA Letters –**FDA letters for IND and IDE studies when applicable.
- **Grant Application and Award Notice** - For research supported by an external grant, a copy of the grant application and award notice (if required by sponsor).
- **Billing Determination and Schedule of Events** – For all research with billable clinical charges.
- **Recruitment materials –** Advertisements (e.g., flyers, posters, website, or social media messages), MyChart messages, letters, emails, phone screening scripts and other subject recruitment materials.
- **Questionnaires, surveys, interview scripts, diaries** or other documents used during the study.
- **Participant informational sheets,** brochures, and sponsor newsletters.
- **Reports submitted for reportable events and information to the IRB. D**
- **Data and Safety Monitoring Board (DSMB) reports, Annual Progress reports** – Submitted with the continuing review report if no additional risks or safety issues identified.
- **Conflict of Interest (COI) Management Plans** as required by an individual's COI Management Plan.
- **Correspondence and communication** between IRB staff, IRB reviewers, IRB members, and investigators and study team members**.**
- **Other IRB correspondence** related to the research**.**
- **Documentation of all actions** including approvals, disapprovals, waivers or alterations of consents and HIPAA authorizations (as documented in the study submission forms).
- **Letters (including Approval letters, Recommendation for Modification, Deferrable, or Notice of Exempt Determination)** for research subject to exempt review.
- **Documentation of protocol closeout if any, including Final Report Form.**
- **All Reminder Notices,** including Expiration notices.
- **IRB approvals from collaborating institutions** as required per Geisinger Single IRB and Ceding processes.
- **IRB Reviewer Sheets and checklists** including Protocol, Reviewer, Informed Consent, Exemption Eligibility, Expedited Eligibility, Expedited Modification Checklist, and Continuing Review checklists, which includes actions recommended by the assigned reviewer.
- **IRB Documentation** – Record of initial and continuing review of research by the expedited review procedure including:
    - Justification for using the expedited procedure rationale for requiring ongoing continuing review when the study otherwise meets criteria for removing the requirement for continuing review
    - Actions taken by the reviewer
    - Any findings required by laws, regulations, codes, and guidance to be documented.

Research Determination Worksheet (RDW)

Effective, August 1, 2018, the Research Determination Worksheet (RDW) and supporting documents of proposed research/project submitted and reviewed by IRB staff for a determination of whether the project includes human subjects research are maintained within the iRIS electronic IRB system. RDWs submitted prior to this date were submitted and maintained outside of iRIS in a separate paper file in the IRB Office.

Other IRB-related Information

Other information is maintained by the IRB, such as correspondence between the IRB and outside agencies and institutions, IRB convened meeting documentation - minutes, minutes lists, agenda, and agenda lists, information about IRB Members (i.e., contact information, background and experience, curriculum vitae, affiliation with Geisinger).

8.2 Record Retention

*The IRB maintains a complete set of materials relevant to the review of the research protocol or plan for a period sufficient to comply with legal and regulatory requirements, Sponsor requirements, and organizational policies and procedures. (**AAHRPP Element II.5.A**)*

In accordance with the Common Rule and FDA regulations (45 CFR 46.115(b)) and 21 CFR 56.115(b)), IRB protocols and all other records are retained for at least three years after the completion of the research, either electronically or as hard copy. This policy applies to all research studies, whether or not participants were enrolled. Records are accessible for inspection and copying by authorized representatives of federal agencies or departments at reasonable times and in a reasonable manner.

Other documents, such as meeting agendas and meeting minutes are maintained either electronically within iRIS or as hard copy in the IRB storage room.

See Guidance Retention of and Access to Research Data.

Maintenance of and Access to IRB Records

All paper (hard) copies of IRB records are secured in closed filing cabinets in locked buildings with regular security and alarms. Records of closed protocols are stored the same until time of destruction. Access to those materials are readily accessible, if necessary.

All electronic copies of IRB records are housed within the iRIS electronic IRB system which resides on a secured server, with password-protected, role-based access. Access to IRB records is routinely provided to the IRB Chair(s), IRB members, IRB staff, and ORC staff to carry out HRPP operations. Access by research investigators and their study team is limited to files related to their own research.

All other Geisinger access to IRB records is limited to those with a legitimate need for access determined on a case-by-case basis.

8.3 IRB Minutes

*The IRB documents discussions and decisions on research studies and activities in accordance with legal and regulatory requirements, Sponsor requirements (if any), and organizational policies and procedures. (**AAHRPP Element II.5.B**)*

The IRB meeting decisions and findings are documented through the IRB minutes. All IRB decisions are documented in the protocol file, which would contain the IRB reviewer sheets, letters, and any correspondence.

*The IRB or EC has and follows written policies and procedures to conduct reviews by the convened IRB: (**AAHRPP Element II.2.D**)*
***Element II.2.D.1**. – Initial review*
***Element II.2.D.2.** – Continuing review*
***Element II.2.D.3.** – Review of proposed modifications to previously approved research*

The IRB minutes document:

- Meeting attendees and invitees, including IRB members, alternate members, ex-officio members, guests, and staff
- Non-Scientific member at the start of the meeting
- Unaffiliated member(s)
- Chair of the meeting
- Each attending member's mode of attendance – in person or via telephone
- The names of IRB members who leave the meeting because of a conflict of interest along with the fact that a conflict of interest is the reason for the absence
- Discussions and actions taken by the IRB and the separate deliberations for each action
- Determinations made by the IRB and the protocol-specific findings that justify those determinations
- If disapproved, the basis for disapproving the research
- Votes for each action recorded as numbers for, opposed, abstaining and recusing (includes names of members who recuse themselves)
- If research involves an experimental device, documentation for the rationale for significant risk/non-significant risk determination
- Other issues requiring convened IRB review

Attendance at an IRB Convened Meeting
Attendance at an IRB convened meeting is recorded in the minutes by documenting:

- The IRB members (voting, non-voting, and ex-officio) who are in attendance
- Each attending member's mode of attendance – in person or via Teams videoconference
- When an alternate member replaces a primary member and is voting at the convened meeting
- The continued presence of quorum for all votes, including a member whose primary concern is in a nonscientific area
- The IRB members who leave the meeting because of a conflicting interest
- The IRB members who leave the meeting briefly, are not present during a vote, and are not counted as part of the quorum
- The IRB members who arrive late or depart early from the meeting and arrival or departure times
- Any others present (e.g., invited guests, investigators invited to address the IRB, consultants)

Discussions
All members attending the convened meeting, regardless of voting status, may actively and equally participate in all discussions. Each submission is reviewed, and any actions taken by the IRB, and the separate deliberations and basis for each action, including controverted issues are documented in the minutes.

Determinations
Final IRB determinations, as applicable, that are made by the IRB are recorded in the minutes with documentation of the protocol-specific findings justifying those determinations as appropriate, such as:

- Approval of research – including the approval period for research, at initial and continuing review
- Approval of research contingent on specific minor conditions, and the designee (staff or IRB member) appointed to review the investigator's submission response and determine whether the condition is satisfied. If the condition is met after the minutes for that meeting is approved, the approval is documented in the minutes of the first IRB meeting that takes place after the contingency is met.
- Determination of the level of risk
- Determinations of serious or continuing non-compliance
- Determinations of unanticipated problems involving risks to participants
- Determinations related to research involving adults with impaired decision-making
- Significant risk and non-significant risk device determinations, pursuant to:
  - 21 CFR 812.2(b)
  - 21 CFR 812.150(b)(9)
  - And considering:
  - FDA Information Sheet– Significant Risk and Nonsignificant Risk Medical Device Studies
  - Geisinger Guidance – IRB Review of Medical Device Research
- Approval for waiver or alteration of informed consent, pursuant to:
  - 45 CFR 46.116(e)
  - 45 CFR 46.116(f)
- Approval for waiver of informed consent documentation, pursuant to:
  - HHS - 45 CFR 46.117(c)
  - FDA - 21 CFR 56.109(c)(1)
- Approval for use of short form process for consent:
  - HHS - 45 CFR 46.117(b)(2)
  - FDA - 21 CFR 50.27(b)(2)
- Approval for waiver of or alteration to HIPAA Authorization, pursuant to:
  - 45 CFR 164.512(i)(1)(i)
- Approval for waiver of documentation of HIPAA Authorization for recruitment or screening, pursuant to:
  - 45 CFR 164.512(i)(2)(ii)

When research involves children, the following IRB decisions are documented pursuant to:

- OHRP approval criteria for Subpart D – Additional Protections for Children as Subjects in Research:
  - 45 CFR 46.404 - Research not involving greater than minimal risk
  - 45 CFR 46.405 – Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

    - 45 CFR 46.406 – Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition
    - 45 CFR 46.407 – Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children
- FDA approval criteria for Subpart D – Additional Protections for Children as Subjects in Research are met when the research is FDA-regulated:
    - 21 CFR 50.51 - Research not involving greater than minimal risk
    - 21 CFR 50.52 – Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
    - 21 CFR 50.53 – Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition
    - 21 CFR 50.54 – Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children
    - 21 CFR 50.55 – Requirements for permission by parents or guardians and for assent by children
        - Determinations about whether assent is necessary or can be waived for some or all children in the clinical investigation
        - Determinations about whether adequate provisions are made for soliciting the assent of children capable of providing assent
        - Requirements for parental permission (See *Geisinger Guidance - Parental Permission*)
            - 21 CFR 50.51 and 50.52 – permission from one parent/guardian
            - 21 CFR 50.53 and 50.54 – permission from both parents/guardians unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child
- Determinations about participation of children who are wards of the state pursuant to:
    - OHRP - 45 CFR 46.409
    - FDA - 21 CFR 50.56

When research involves pregnant women, fetuses, and neonates, the following IRB decisions are documented pursuant to OHRP approval criteria for Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research:

- 45 CFR 46.204 – Research involving pregnant women or fetuses
- 45 CFR 46.205 – Research involving neonates
- 45 CFR 46.206 – Research involving, after delivery, the placenta, the dead fetus, or fetal material
- 45 CFR 46.207 – Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates

Currently Geisinger does not conduct prisoner research. If prisoner research were to be conducted, IRB membership would be modified to include prisoner representation and determinations related to approval of research involving prisoners as participants would be reviewed and documented pursuant to Subpart C – Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Other Issues

Other issues are documented in the minutes, including but not limited to:

- IRB review and approval of previous convened IRB meeting minutes
- IRB approval of research reviewed at a previous convened meeting, approved with minor modifications, and documented in the previous meeting's minutes as such. Final approval of that research was contingent on the investigator's satisfactory response to specific minor conditions as determined by the chair or designee. As that review and approval takes place via administrative review outside of a convened meeting. That approval is documented in the minutes
- Presentation of information from an outside consultant or expert as requested by the IRB
- IRB review and approval of humanitarian use devices per
- The names of IRB members who abstain for reasons other than conflict of interest
- Training or presentation presented to IRB members during a convened meeting
- Other items as applicable

Disposition of the IRB Minutes

The IRB staff members compose the minutes and make them available for IRB review and approval as soon as possible. Minutes may not be altered by anyone including a higher authority once approved by the members during a convened IRB meeting. If revisions are necessary because of an identified error, the revised minutes will be reviewed and approved at a subsequent convened meeting.

The minutes of convened IRB meetings are considered confidential and access to minutes is restricted and secured in the iRIS electronic IRB system with access only to IRB staff and members. Requests for disclosure of IRB meeting minutes for other purposes (e.g., accreditations) will be considered on a case-by-case basis by Director, IRB Operations &HR

Section 9 - Risks to Research Participants

9.1 Minimizing Risk

*The IRB has and follows written policies and procedures for identifying and analyzing risks and identifying measures to minimize such risks. The analysis of risk includes a determination that the risks to participants are reasonable in relation to the potential benefits to participants and to society. (**AAHRPP Element II.3.A**)*

HRPP policies related to risk assessment are based on both the 2018 Common Rule (45 CFR 46.111) and FDA regulations (21 CFR 56.111). When reviewing study submissions, the IRB analyzes and assesses levels of risk, ensures risks are minimized, and ensures risks are reasonable relative to anticipated benefits, before approving the proposed research.

To approve research, the IRB determines:

- Research studies have the resources necessary to protect participants:
  - Adequate time for the researchers to conduct and complete the research.
  - Adequate number of qualified staff
  - Adequate facilities
  - Access to a population that will allow recruitment of the necessary number of participants.
  - Availability of medical or psychosocial resources that participants might need because of the research.

DEFINITIONS:
Risk in the context of human subjects' research refers to the combination of the probability and magnitude of some future harm or injury (physical, psychological, social, or economic) occurring because of participation in a research study. Both the probability and magnitude of possible harm may vary independently and result in risks that range from "extremely high" to "low" depending on whether they are more (or less) likely to occur, and whether the potential harm is more (or less) serious.

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. (HHS - 45 CFR 46.102(j); FDA - 21 CFR 56.102(i)). For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is minimal because it is comparable to risk of doing so as part of routine physical examination.

Risk Level Definitions for IRB Review/Determination

Extremely High Risk: Activities containing unacceptable levels of risk, including catastrophic and critical injuries that are highly likely to occur. Determine whether the risks can be eliminated or modify activities after applying all reasonable risk management strategies.
High Risk: Activities containing potentially serious risks that are likely to occur. Proactive application of risk management strategies to reduce the risk should occur. Determine ways to modify or eliminate unacceptable risks.
Moderate Risk: Activities containing some level of risk that is neither likely nor serious in magnitude. Determine what can be done to manage the risk to prevent any negative outcomes.
Low Risk: Low risk activities are minimal risk activities. The activities can proceed as planned.

Identifying and Analyzing Potential Risks

The PI should describe in the study submission:

- Risks to participants, including an evidence-based estimate of the probability, frequency, severity, and reversibility. Use Figure 2 on the following pages for guidance.
- The statistical incidence of complication and the mortality rate of the proposed procedure, if known.
- The planned procedures for protecting against or minimizing potential risks, including risks to confidentiality. Two plans are necessary:
    - ensure necessary medical or counseling intervention in the event of harm to participants
    - ensure the safety of participants and the validity and integrity of research data. Data and safety monitoring must be commensurate with risks and the size and complexity of the trials.

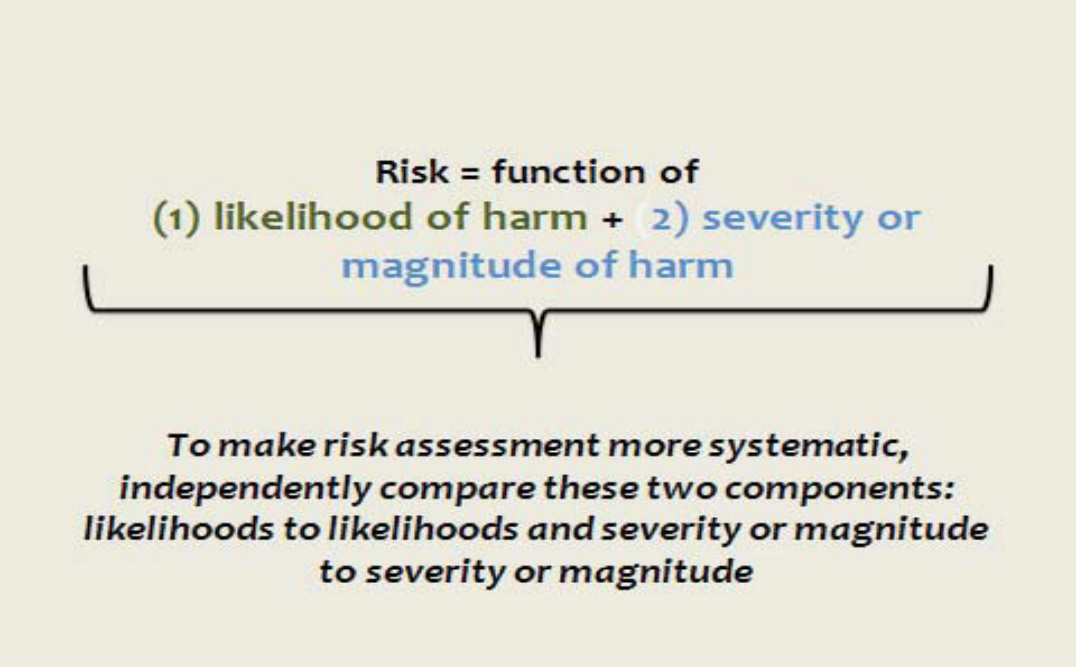
When proposing changes to the research, PIs must submit an Amendment/Modification form an include a description of and rationale for the proposed changes and assessment of the impact of the proposed changes on the level of risk and potential benefits.

Ensuring Risks Are Adequately Assessed and Minimized

The diversity of scientific disciplines represented by the IRB membership *(*see *Section 6- Structure and Composition of the IRB*) allows for a critical assessment of research protocols. The IRB considers the risk to participants in evaluating the proposed research in accordance with the conditions outlined in 45 CFR 46.111 and 21 CFR 56.111(a)(1-7) and the ethical principles outlined in the Belmont Report. Furthermore, the IRB may consult with additional experts as needed.

The IRB should independently compare both the likelihood or probability of harm and the severity or magnitude of harm.

Fgure 1



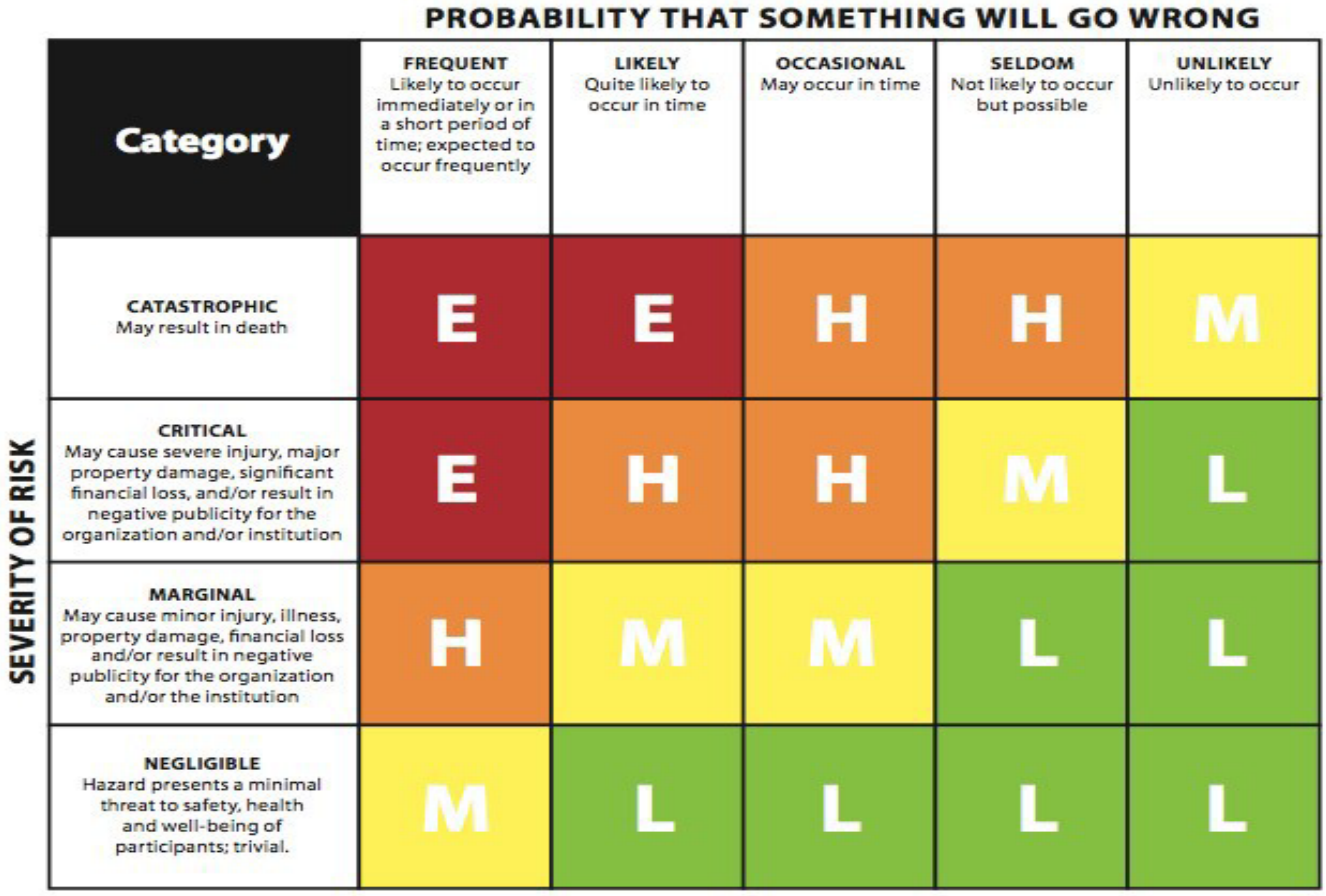
Before approving a research protocol, the IRB must determine that risks are minimized as follows by:

- Ensuring that the proposed research has a sound research design
- Ensuring that the research does not expose subjects to unnecessary risks, and
- Whenever appropriate, utilizing procedures that are already being performed on the subjects for diagnostic or treatment purposes.

The IRB examines the study submission, including research design and methodology, to determine that there are no inherent flaws that would place research participants at unnecessary risk. This includes the risk that research lacking in statistical power may not lead to meaningful results.

Appropriate safeguards can also minimize risk to participants (e.g., adequate data monitoring plan to monitor risks to participants or protecting confidentiality by using coded data). If risks are not adequately minimized, the protocol will not be approved as written. See *Geisinger Guidance - Evaluating Sound Study Design.*

Figure 2



E = Extremely High; H = High Risk; M = Moderate Risk; L = Low Risk

The IRB also considers the professional qualifications and resources (including time, equipment, support services) of the research team to protect participants and minimize potential harm. Research personnel must have received appropriate training, and clinicians involved in the research must maintain appropriate professional credentials and licensing privileges. The PI attests to presence of adequate resources to conduct the research when signing each study submission to the IRB in the iRIS Geisinger Investigator Assurance.

Risks v. Anticipated Benefits

The study protocol should describe anticipated benefit(s) that may be gained by participants, and how the knowledge gained may benefit the participants, future participants, or society. The investigator should explain how these potential benefits to the participant or society outweigh the risks inherent in the research.

The IRB determines whether the risks of the research are reasonable in relation to the anticipated benefits (if any) to research participants and the importance of the knowledge that may reasonably be expected to result. (HHS - 45 CFR 46.111; FDA - 21 CFR 56.111)

The IRB bases its risk/benefit analysis and assessment on the information provided by the PI and on the expertise of its members and consultants who utilize the most current information about the risks and benefits of the interventions involved in the research.

The IRB considers only those risks that result from the research and does not consider long-range effects (e.g., public policy implications) of applying the knowledge gained in the research. The IRB does not consider those risks and benefits that participants would receive even if not participating the research.

9.2 Data Monitoring Plan

*The IRB has and follows written policies and procedures for reviewing the plans for data and safety monitoring, when applicable, and determines that the data and safety monitoring plan provides adequate protection for participants. (**AAHRPP Element II.3.B**)*

To approve research, the IRB must determine that, where appropriate, the research plan makes adequate provisions for monitoring the data to ensure the safety of research participants. (HHS - 45 CFR 46.111; FDA - 21 CFR 56.111)

More than minimal risk studies must include a Data Monitoring Plan. Investigators are required to describe the Data Monitoring Plan in the study submission. :

- The Data Monitoring Plan must be commensurate with the level of risk, size, and complexity of the study.
- The Data Monitoring Plan might need to include a DSMB (data safety monitoring board) or DMC (data monitoring committee). A DSMB or DMC may be required as part of the monitoring plan by NIH, FDA, other sponsors, or the IRB.
- All clinical trials require monitoring, including physiologic, toxicity, and dose-finding studies (Phase I); efficacy studies (Phase II); efficacy, effectiveness, and comparative trials (Phase III).

The data safety monitoring plan for greater than minimal risk studies involve IRB review of the details regarding the safety and protection of data. This could include the review and consideration of the following:

- What safety information will be collected, including serious adverse events?
- How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).
- The frequency of data collection, including when safety data collection starts.
- The frequency or periodicity of review of cumulative safety data.
- The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor, including the frequency of reporting.

- For studies that do not have a data monitoring committee and are blinded, have multiple sites, enter vulnerable populations, or employ high-risk interventions, the IRB needs to carefully review the data and safety monitoring plan and determine whether a data monitoring committee is needed.
- If not using a data monitoring committee, and if applicable, statistical tests for analyzing the safety data to determine whether harm is occurring.
- Provisions for the oversight of safety data (e.g., by a data monitoring committee).
- Conditions/criteria that trigger an immediate suspension of the research, if applicable.

Refer to additional resources for detailed information on what a data monitoring plan might address, when a data monitoring plan is required, and when a data monitoring board or committee is required:

- HRPP Handbook Section 15 – Investigator Requirements
- *Geisinger Guidance - Data and Safety Monitoring*
- Data Monitoring Committees - *Guidance for Clinical Trial Sponsors - Establishment and Operation of Clinical Trial Data Monitoring Committees (March 2006)*
- Data Monitoring Plans and Data Monitoring Committees – NIH and NCI policies:
  - *NIH: Policy for Data and Safety Monitoring*
  - *NIH: Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials*
  - *POLICY OF THE NATIONAL CANCER INSTITUTE FOR DATA AND SAFETY MONITORING OF CLINICAL TRIALS (Published 7/15/2020)*

The IRB does not perform data monitoring, but ensures that appropriate monitoring is taking place, and reviews reports from the monitoring entity.

The IRB must ensure that the conditions for initial IRB approval of the research are still satisfied at continuing review. These include, but are not limited to, determinations by the IRB regarding risks, potential benefits, informed consent, and safeguards for participants. Thus, the PI must include in the continuing review report the outcomes of data and safety monitoring, any Unanticipated Problems, and any new information pertaining to the research - either from the research itself or from other sources, which have occurred since the previous IRB review. A copy of any data and safety monitoring reports must be attached to the continuing review report; therefore, a copy is available for review in its entirety. The amount of detail required depends on the type of research being conducted. In many cases, an appropriate summary would be a simple brief statement that there have been no Unanticipated Problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and any investigator brochure.

Whether the method of monitoring is by PI oversight or from the establishment of a DSMB, the IRB can tailor a specific timeframe for future reporting of data monitoring findings to the IRB. The IRB can set the date of continuing review for the protocol as being less than the maximum of a year (for studies with a continuing review requirement), if the IRB determines that interim reporting of data monitoring information will serve to better protect participants. Alternatively, the IRB can request a report after a specific number of participants are enrolled or after a serious adverse event has been reported.

9.3 Risks to Vulnerable Populations

*The IRB has and follows written policies and procedures for determining the risks to prospective participants who are vulnerable to coercion or undue influence and ensuring that additional protections are provided as required by applicable laws, regulations, codes, and guidance. (**AAHRPP Element II.4.A**)*

The IRB is cognizant of the vulnerable nature of many participants. Food and Drug Administration (FDA) regulations and the 2108 Common Rule require IRBs to give special consideration to protecting the welfare of vulnerable populations.

To approve research involving vulnerable populations, the IRB must determine, where appropriate, that additional safeguards have been included to protect the rights and welfare of participants who are likely to be vulnerable to coercion or undue influence, such as:

- Children, pursuant to:
  - OHRP - 45 CFR 46 Subpart D – Additional Protections for Children as Subjects in Research
  - FDA - 21 CFR 50 Subpart D – Additional Protections for Children as Subjects in Research
- Pregnant women, human fetuses, or neonates, pursuant to: 45 CFR 46 Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
- Persons with impaired decision-making
- Economically or educationally disadvantaged persons
- Employees
- Students

The IRB includes among its members' persons who are knowledgeable about and experienced in working with vulnerable participants (45 CFR 46.107(a); 21 CFR 56.107(a)). When a research study involves a vulnerable population not otherwise covered by these policies, the IRB takes steps to evaluate whether additional safeguards have been included in the research to protect the rights and welfare of participants.

(See Section 12.2 - Consent Procedures for Vulnerable and Other Special Populations Including Consent by a LAR) for consent procedures for vulnerable populations.

Considerations in Reviewing Research involving Vulnerable Participants

The IRB considers the following elements of the research plan when reviewing research involving vulnerable participants:

- *Strategic issues* that involve inclusion and exclusion criteria for selecting and recruiting participants; informed consent and willingness to volunteer; coercion and undue influence; and confidentiality of data.
- *Group characteristics*, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable participants.
- *Participant selection to prevent over-selection or exclusion* of certain participants based on perceived limitations or complexities associated with those participants. For example, it is not appropriate to target prisoners as research participants merely because they are a readily available "captive" population.

- *Application of state or local laws* that bear on the decision-making abilities of potentially vulnerable populations. State statutes (as discussed in Handbook - Section 12) often address issues related to competency to consent for research, emancipated minors, legally authorized representatives (LAR)s, the age of majority for research consent, and the waiver of parental permission for research.
- ***Procedures* for assessing and ensuring participants' capacity, understanding, and informed consent or assent. The** study application requires investigators to describe their plan to assess individuals' ability to provide informed consent**. In certain instances, it may be possible for investigators to enhance understanding for potentially vulnerable participants.** Examples include requiring someone not involved in the research to obtain the consent, the inclusion of a consent monitor, a participant advocate, interpreter for hearing- impaired participants, translation of informed consent forms into languages the participants understand and reading the consent form to participants slowly and ensuring understanding paragraph by paragraph.
- *Need for additional safeguards* to protect potentially vulnerable populations. For example, the IRB may require a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

For information about recruitment of vulnerable populations, see:

- HRPP Handbook Section 12.7 - *Observation of the Consenting Process*
- Geisinger Guidance – Recruitment with Vulnerable Participants

Children

The IRB follows the requirements of the DHHS regulations at 45 CFR 46, Subpart D and FDA regulations at 21 CFR Part 50, Subpart D in reviewing protocols involving children. The IRB makes the findings and determinations required by the DHHS and FDA regulations related to the risks before allowing research involving children to proceed. The additional protections detailed in this section must be followed for research protocols that include children as human subjects.

Informed Consent

- [DHHS and FDA] 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. Additional protections for children described here must be applied only if an individual involved in the research meets this definition.

- [Pennsylvania law] The legal age for consent to treatments or procedures involved in research is 18, but there are important exceptions. These exceptions are outlined in ***Geisinger Permissions and Informed Consent Policy***.

Limits on Exemption Determinations Related to Children

Research protocols involving children shall not be eligible for exemption from IRB review pursuant to:

- Exemption Category 2 (45 CFR 46.104(d)(2)) - research involving survey or interview procedures or observations of public behavior, except for research involving the observation of public behavior when the investigators do not participate in the activities being observed.
- Exemption Category 3 (45 CFR 46.104(d)(3)(i)) - Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written

responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection

IRB Determination of Applicable Children's Category Required

In addition to other responsibilities assigned to the IRB for research protocol review, in conducting review of proposed research involving children, the IRB may approve only research involving children that fits all the requirements set forth below for four permissible categories. Depending on the type of research being reviewed, the Geisinger IRB, in addition to performing its standard review, shall be required to make the following additional findings per DHHS Subpart D – Additional Protections for Children as Subjects in Research and FDA Subpart D – Additional Protections for Children as Subjects in Research (when the research is FDA-regulated).

1. Minimal Risk Research
2. Minimal Risk Research is research that does not involve physical or emotional risk greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests. To approve a research protocol of this type, the Geisinger IRB must determine and document in its meeting minutes and/or review documents that the protocol:
    a. Is reviewed pursuant to 45 CFR 46.404, and pursuant to 21 CFR 50.51 if an FDA- regulated product is involved;
    b. Presents only minimal risk to the children who are enrolled; and
    c. Provides for obtaining the assent of the children and the permission of their parents or legal guardians. The IRB shall determine if adequate provisions attaining assent are included and shall decide if the permission of one parent or legal guardian is sufficient to safeguard the child or if the permission of both parents is required.
3. Research with More than Minimal Risk that Presents Prospect of Direct Benefit to Participants
4. To approve a protocol of this type, the Geisinger IRB must determine and document in its meeting minutes and/or review documents that the protocol:
    a. Is being reviewed pursuant to 45 CFR 46.405 and pursuant to 21 CFR 50.52 if an FDA regulated product is involved;
    b. Poses risk to the subjects that is justified by the anticipated benefit to the subject.
    c. Presents anticipated benefit in relation to the risk that is at least as favorable to the subject as that provided by available alternative approaches; and
    d. Provides for obtaining the assent of the children and the permission of their parents or legal guardians. The IRB shall determine if adequate provisions attaining assent are included and shall decide if the permission of one parent or legal guardian is sufficient to safeguard the child or if the permission of both parents is required.
5. Research Involving More than Minimal Risk and No Prospect of Direct Benefit to Individual Subjects, but Likely to Yield Generalizable Knowledge about the Subject's Disorder or Condition
6. To approve this type of research protocol, the Geisinger IRB must determine, and document in its meeting minutes and/or review documents, that:
    a. The research protocol is being reviewed pursuant to 45 CFR 46.406 and pursuant to 21 CFR 50.53 if an FDA-regulated product is involved;
    b. That the risk of the research protocol is just a minor increase over minimal risk.

7. That the intervention or procedure presents experiences to the subject that are reasonably commensurate with those inherent in their actual, or expected medical, dental, psychological, social, or educational situations.
8. That the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the disorder or conditions; and
9. That the research protocol provides for obtaining the assent of the children and the permission of their parents or legal guardians. Both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
10. Research that Cannot be Approved under 45 CFR 46.404, 405 or 406 but that Presents a Reasonable Opportunity to Further the Understanding, Prevention or Alleviation of a Serious Problem Affecting the Health or Welfare of Children
11. This type of research protocol requires approval by both the IRB and OHRP if the protocol is subject to DHHS regulation, and by the FDA, if the research protocol involves an item regulated by the FDA.
12. Before an IRB can submit a research protocol in this category to OHRP and/or to the FDA for review, it must make and document in meeting minutes and/or review documents the following findings:
    a. That the research protocol is appropriately being reviewed pursuant to 45 CFR 46.407 and pursuant to 21 CFR 50.54 if an FDA regulated product is involved.
    b. That the research protocol does not meet the conditions for approval under 45 CFR **Sections 46.404, 405 or 406**, or under 21 CFR 50.51, .52 or .53 if an FDA regulated product is involved.
    c. That the research protocol provides for obtaining the assent of the children and the permission of their parents or legal guardians.
    d. Both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. That the research protocol, including all assent and parental permission forms, comply with all with all other applicable regulatory requirements set forth in 45 CFR 46.111, .408 and .409, and in 21 CFR 50.55, .56 and 56.111, and any changes to the protocol and consent/assent documents requested by the IRB are incorporated.

OHRP Submission for 45 CFR 46.407 Research Subject to HHS Regulation:

For OHRP to determine whether review under Section 46.407 may proceed, the IRB in conjunction with the PI shall submit the following documents (in both hard copy and electronic format, if possible) to OHRP, Division of Policy and Assurances, Department of Health and Human Services, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852:

- Documentation of required IRB findings that protocol does not qualify for review under 45 CFR 46.404, 405 or 406, but does meet review requirements of 407.
- Name of institution and IRB, along with assurance number for IRB.
- IRB contact person's name, title, phone number, fax number, mailing address and email address.
- Title of protocol and name of PI.
- HHS application number and name of funding agency. Relevant HHS grant application or proposal.
- Most current version of protocol and grant application submitted to, reviewed by the IRB, and modified by the principal investigator if required by the IRB.

- Most current version of parental permission/assent documents submitted to, reviewed by the IRB, and modified by the PI if required by the IRB.
- Relevant IRB minutes and correspondence.

OHRP and FDA Approval of 45 CFR 46.407 Research that is Federally Supported
Expert panels established by OHRP and FDA (if an FDA regulated item is involved) must review and approve research in this category after seeking public comments on the research through the federal register and holding a meeting of the panel.

Non-Federally Supported 45 CFR 46.407 Research
If the IRB reviews research not subject to HHS jurisdiction that cannot be approved under 45 CFR 46.404, 405 or 406 but 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 determine whether it wishes to seek the opinion of consultants before making its final decision whether to approve the project.

Persons with Impaired Decision-Making Capacity
The IRB reviews the risk-benefit analysis including the possibilities of coercion and undue influence and must determine whether such individuals should be recruited and whether support mechanisms, such as surrogate consent, are appropriate. *(*See *Section 12.2- Consent Procedures for Vulnerable and Other Special Populations Including Consent by a LAR)* for more information on the consent process, and criteria for including persons with impaired decision making in research.

Pregnant Women, Human Fetuses, and Neonates
The Department of Health and Human Services (DHHS) details special protections for research involving pregnant women, human fetuses, and neonates in Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research. Under these regulations, the IRB is required to document specific findings to minimize the potential for risk or harm to the pregnant women, fetuses, and neonates. Additional attention must be given to the conditions for obtaining informed consent, in accordance with these regulations. See also, ***Geisinger Guidance - Research Involving Pregnant Women, Fetuses, and Neonates*.**

In general, Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research requires that research involving pregnant women, human fetuses, and neonates should involve the least possible risk. Persons engaged in the research may have no part in the timing, method, or procedures used to terminate the pregnancy, or to determine the viability of the fetus. No inducements may be offered to terminate a pregnancy.

Separate conditions for research with this population, each with their own requirements and IRB determinations, are detailed in Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research:

1. *Research Involving Pregnant Women.* Pregnant women may not be involved as participants in research unless either of the following conditions applies: The purpose of the activity is to meet the health needs of the mother, and the fetus is placed at risk only to the minimum extent necessary to meet such needs; OR the risk to the fetus is minimal. The mother and the father must be legally

competent and provide consent, unless the purpose of the research is to meet the health needs of the mother, or the father is not reasonably available, or the pregnancy resulted from rape.

2. *Research Directed at Human Fetuses*. The IRB must find that: the purpose of the research is to meet the health needs of the individual fetus and shall be conducted in a way that will minimize risk; OR the research will pose no more than minimal risk to the fetus, and the purpose of the activity is to ascertain important biomedical knowledge that is unobtainable by other means. These activities are permitted only if the mother and father are legally competent and have given informed consent, unless the father is not reasonably available, or the pregnancy resulted from rape.
3. *Research Involving Neonates*. For research involving neonates, the IRB must distinguish between viable and non-viable neonates. Viable is defined in the regulations as being able to survive to the point of independently maintaining a heartbeat and respiration, given the benefit of available medical therapy. If the neonate is viable, it is considered a "child" and may be involved in research to the extent permissible under DHHS Subpart D – Additional Protections for Children as Subjects in Research.
    - *A non-viable neonate* may not be involved in research unless all the following conditions apply: The vital functions of the neonate are not artificially maintained; experimental activities that would of themselves terminate the heartbeat or respiration are not employed; AND the purpose of the research is development of important biomedical knowledge that cannot be obtained by other means. Research involving a non-viable neonate is permitted only when both parents have given informed consent, unless one parent is not reasonably available, or the pregnancy resulted from rape or incest. In the case of non-viable neonates, consent by a parent's LAR is not allowed.
    - *A neonate of uncertain viability* may not be involved in research unless one of the following conditions applies: There is no added risk to the neonate and the purpose of the research is to obtain important biological knowledge that cannot be obtained by other means; OR the purpose of the activity is to enhance the probability of survival of the individual neonate. Research involving a neonate of uncertain viability is permitted only if either parent or the parent's LAR gives permission.

Non-pregnant women of reproductive potential

Unilateral exclusion of non-pregnant women of reproductive potential from research is not permitted by the IRB. Exclusion requires compelling scientific justification. Where such justification exists, it may also be appropriate to exclude men of reproductive potential.

Other Potentially Vulnerable Participants

The context of the research is an important consideration for the IRB when reviewing research that involves other potentially vulnerable participants such as research involving homeless persons, members of particular minority groups, or the economically or educationally disadvantaged. Research involving significant follow-up procedures or offering significant monetary compensation may unduly influence certain types of participants, and the IRB takes such considerations into account. Nevertheless, inclusion of individuals from diverse socioeconomic, cultural, racial, and ethnic backgrounds impacts the ability to develop treatments and care strategies that are impactful to all of society and not just a select population. Therefore, inclusion of diverse participants is socially important for understanding and eventually improving the health and general well-being of these populations.

Employees and Students
Employees, including but not limited to physicians, fellows, residents, research personnel, lab personnel, students, and trainees at Geisinger and other facilities under the purview of the IRB are considered vulnerable participants, in particular because of the risk of coercion and undue influence. The IRB has the same standards for approving research involving these groups as other vulnerable participants.

Prisoners
****Currently Geisinger IRB is not constituted to review studies planning to enroll Prisoners.*** If prisoner research were to be conducted, IRB membership would be modified to include prisoner representation and determinations related to approval of research involving prisoners as participants would be reviewed and documented pursuant to Subpart C – Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects.

If an enrolled participant becomes incarcerated/prisoner, please contact the IRB for guidance.

9.4 Suspension or Termination of IRB approval

*The IRB has and follows written policies and procedures for suspending or terminating IRB approval of research, if warranted, and for reporting these actions, when appropriate. (**AAHRPP Element II.2.G**)*

The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and HHS department or agency head (HHS - 45 CFR 46.113) and/or the Food and Drug Administration for FDA-regulated research (FDA - 21 CFR 56.113).

DEFINITONS:

Suspension: Temporary withdrawal of IRB approval for some or all research procedures in a protocol or the permanent withdrawal of IRB approval of the research. Continuing review of the research is still required. A sponsor-imposed suspension alone does not constitute such a suspension, as it is not an action by the IRB to withdraw approval of a previously approved protocol. Similarly, an action by the Principal Investigator (PI) that halts or materially changes some or all the PI's protocol as previously approved by the IRB does not constitute such a suspension (but must be submitted to the IRB as a protocol amendment/modification).

Termination: Permanent withdrawal of IRB approval of previously approved research.

Suspension or Termination by the IRB

Suspension or Termination Procedure

The convened IRB may act to suspend or terminate a protocol for any of the following reasons including, but not limited to:

- Not conducting research in accordance with IRB requirements
- Unexpected serious harm to subjects

IRB Chair(s) have the authority to temporarily suspend or terminate research on an urgent basis until the submission can be reviewed at a convened meeting. The IRB staff add the suspension/termination to the agenda of the next scheduled meeting where the convened IRB will review it.

The IRB Chair shall:

- Notify the PI in writing of it the IRB decision to suspend or terminate its approval along with a statement of the reasons for the IRB action and any terms and conditions of any suspension.
- Report the decision to suspend or terminate to appropriate institutional officials, and HHS department or agency head (HHS - 45 CFR 46.113) and/or the Food and Drug Administration for FDA-regulated research. (FDA - 21 CFR 56.113)

The PI can appeal the IRB's decision and must respond in person or in writing to the IRB regarding a suspension or termination.

If the IRB action in relation to the suspension or termination involves the withdrawal or modification of participation of current participants from the research, the IRB shall direct the PI to contact the participants and sponsors to:

- Make such notification with an explanation, after its review and approval by the IRB
- Make arrangements for withdrawal of investigational product (if applicable) that ensures the safety and welfare of participants
- Describe any monitoring and follow-up that will be conducted for safety reasons
- Provide contact information for the PI and the IRB where the participant may report any adverse events or Unanticipated Problems.

Protection of Participants Who May Be Affected by the IRB Action

If the suspension or termination will affect participants in the protocol (e.g., requires withdrawal of participants), the IRB shall utilize a process that considers the impact on participants' health and safety. This should occur before the suspension or termination, when it is feasible, and delay will not jeopardize participants' health and safety. Examples include:

- Requiring the PI to submit proposed procedures for any withdrawal of participants
- Allowing participants to continue (e.g., treatment with an investigational drug) if the IRB determines that it is in their best interests
- Requiring submission of all communications by the PI to participants about the IRB action for review and approval of the IRB
- Designating an investigator other than the PI to be responsible for carrying out the IRB decision

- Requiring the appointment of a new PI or transferring responsibility for participants to another investigator
- Requiring the PI to carry out follow-up or monitoring of participants appropriate to the circumstances (e.g., for any adverse impact on participants after suspension or termination)
- Requiring special reporting (e.g., adverse events or outcomes) concerning participants by the PI.

Section 10 - Participant Recruitment and Selection

10.1 Equitable Selection

*The IRB has and follows written policies and procedures to evaluate the equitable selection of participants. (**AAHRPP Element II.3.C**)*

Guidance and information are made available to Principal Investigators (PIs) to assist and guide them in creating recruitment and participant selection methods that are fair and equitable. See:

- *Geisinger Guidance - Advertisements Appropriate Language for Recruitment Material*

Investigators are directed to provide information about identification and recruitment of potential participants in the study submission. PIs are required to identify the target populations (including age range, gender, and vulnerabilities), the eligibility criteria and whether payments will be compensated for participation. In addition, PIs are required to justify the inclusion of vulnerable populations. In determining if the selection and recruitment of participants is equitable, the IRB considers the purpose of the research, the setting in which the research will be conducted, whether prospective participants will be vulnerable to coercion or undue influence, the selection (inclusion/exclusion) criteria, participant recruitment and enrollment procedures, and payments to participants. The IRB also evaluates whether the study imposes fair and equitable burdens and benefits - such that one group of persons does not disproportionately receive the benefits compared to another group assuming only the risks.

IRB staff and members review this information and confirm that recruitment and selection strategies are fair, equitable, and not misleading. If recruitment strategies fail to meet these requirements, the protocol will not be approved as written and the PI will be asked to modify the recruitment plan accordingly, as a condition of approval.

Vulnerable Subjects

Investigators must provide a rationale for involvement of vulnerable subjects, such as children, pregnant women, economically and educationally disadvantaged, decisionally impaired, employees, and students. The PI must provide rationale for including a vulnerable population. When vulnerable populations will be targeted for enrollment, the IRB assesses the additional safeguards proposed by the PI to minimize the possible risks and the chance of harm to these populations. While pregnant women are considered vulnerable participants, women of reproductive age should not be arbitrarily excluded from participation in research. If women are to be excluded, such exclusion must be fully justified by the PI based on scientific rationale. The IRB adheres to *Geisinger Guidance - Women as Subjects in Research* when considering women as participants.

Non-English-Speaking Participants

Non-English-speaking participants should not be systematically excluded because of language barriers. The IRB encourages the inclusion of non-English speaking participants and permits such persons to be enrolled either by translation of the consent form in the subjects' native language or via the short form consent process consistent with 45 CFR 46.117(b)(2) and 21 CFR 50.27(b)(2). *(*See *Section 12.1- Requirements for Informed Consent*) for additional details on the short form consent process.

10.2 Review of Recruitment Methods, Advertising Materials and Payment

*The IRB has and follows written policies and procedures to review proposed participant recruitment methods, advertising materials, and payment arrangements and determines whether such arrangements are fair, accurate, and appropriate. (**AAHRPP Element II.3.C.1**)*

Recruitment Methods

Investigators are required to describe all methods of recruitment proposed for the research, including how participants will be identified and approached for recruitment. Some common recruitment methods include recruiting from one's own patients, seeking referrals from colleagues (via word of mouth or referral letters sent to colleagues), and advertisements.

Advertisements

The IRB considers that advertisements begin the informed consent process and thus, consistent with the consent process, coercion and undue influence are prohibited during recruitment. If recruitment will be by advertisement, the mode of advertisement (e.g., flyers, radio, newspaper, websites, social media) and information contained in the advertisement must be approved by the IRB.

- ***Audio and video tape****:* The IRB may review and approve the wording prior to taping to preclude when possible. The IRB reviews the final version of the advertisement.
- ***Advertisement developed by Geisinger research staff:*** Geisinger Marketing & Communications must review geisinger-developed research posters or recruitment advertisements and digital recruitment messaging. Confirmation of the review and approval must be submitted to the IRB.
- ***Printed advertisement developed by clinical sponsors****: P*rinted advertisement that is visible to Geisinger patients must be submitted to the IRB for review and approval.
- ***MyChart Messages****:* Must be submitted to Geisinger's Digital Engagement team for review and approval before submitting to the IRB. Confirmation of their review and approval must be submitted to the IRB.

Also see:

- *Guidance - Advertisements: Appropriate Language for Recruitment Material*
- *FDA Information Sheet – Recruiting Study Subjects: Guidance for Institutional Review Boards and Clinical Investigators (January 1998)*

Payment

PIs must disclose any proposed payments to participants in the study submission, including the method, type, and timing of the payments. Payments to research participants may not be of such an amount as to result in coercion or undue influence on the research participant's decision to participate. If a study has multiple paid visits, payment should be prorated throughout the duration of the study to provide partial payment to persons who withdraw before completing the study.
See:

- *Geisinger Guidance Payment – Ethical Considerations*
- *Geisinger Policy - Payments to Study Participants* outlines a uniform guideline for the management and disbursement of payments to study participants

Prohibited Recruitment and Payment Practices

The following activities are examined carefully and are generally not allowed:

- Exculpatory language through which the participant or participant's LAR is made to waive or appear to waive any of the participant's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

Payment Arrangement among Sponsors/Organizations, Investigators rand Others

Payment in exchange for referrals of potential participants (finder's fees) and payments designed to accelerate recruitment tied to the rate or timing of enrollment (bonus payment) are unacceptable.

Section 11 - Privacy and Confidentiality

11.1 Protecting the Privacy of Participants

*The IRB has and follows written policies and procedures to evaluate the proposed arrangements for protecting the privacy interests of research participants, when appropriate, during their involvement in the research. (**AAHRPP Element II.3.D**)*

Geisinger has established the following written policies, together with the other policies referenced in this section, to protect the privacy of research participants and confidentiality of data.

- To approve research (HHS - 45 CFR 46.111(a)(7) and FDA - 21 CFR 56.111(a)(7)), the IRB must determine thee research plan includes adequate provisions to protect the privacy of participants and confidentiality of data.
- To determine research meets criteria for exemption under Exemption categories 2(iii) and 3(i)(C) at 45 CFR 46.104, an IRB member must conduct a "limited review" and be satisfied that, "when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data" (45 CFR 46.111(a)(7)).
- An invasion of privacy or breach of confidentiality may be a moral wrong or even present a risk of serious harm to participants (e.g., jeopardize their family relationships, community standing, employment, or lead to prosecution for criminal behavior). The IRB reviews each protocol, based on the information submitted by the investigator, and assesses the amount and type of private information involved, how the information will be collected, and plans for its use, maintenance and disclosure. As necessary, the IRB will ask for additional details during its review.

DEFINITIONS:
Privacy means, in the context of a research protocol, respecting an individual's right to be free from unauthorized or unreasonable intrusion, including control over the extent, timing and circumstances of obtaining personal information from or about them. For example, individuals may not want to be seen entering a place that might stigmatize them, such as a clearly identified pregnancy counseling center.

Privacy refers to persons and their interest in controlling the access of others to themselves. To approve research, the IRB must determine that, where appropriate, there are adequate provisions to protect the privacy interests of potential or current participants, from the screening and recruitment through all phases of research. If the protocol does not include adequate provisions to protect the privacy interests of the participants, the IRB may not approve the protocol as written.

The PI must describe in the Study submission the provisions for protecting the privacy of participants during screening, data collection and other interactions. The IRB assesses the information during the review process. As necessary, the IRB will ask for additional details during its review.

Provisions for protecting the privacy interests of participants or participants should include:

- Ensuring that the conditions under which a procedure is performed, or information is collected (e.g., physical locations, telephone contact, mail, or email solicitations) afford protections against

interactions with participants being witnessed, overheard, or inadvertently intercepted or viewed. For example, a potential or current participant may feel uncomfortable:
    - Being seen entering a place that they feel might stigmatize them, such as a pregnancy counseling center.
    - Having physical measurements recorded in a non-private setting.
    - Discussing private medical information in a non-private setting.
    - Answering sensitive questions by telephone while at home or work.
- Limiting the information being collected to only the minimum amount of data necessary to accomplish the research purposes.

11.2 Protecting the Confidentiality of Participant Information

*The IRB has and follows written policies and procedures to evaluate proposed arrangements for maintaining the confidentiality of identifiable data, when appropriate, preliminary to the research, during the research, and after the conclusion of the research. (**AAHRPP Element II.3.E**)*

*Researchers and Research Staff follow the requirements of the research protocol or plan and adhere to Geisinger policies and procedures and to the requirements or determinations of the IRB. (**AAHRPP Element III.2.C**)*

DEFINITIONS:

Confidentiality means respecting a potential or current participant's right to be free from unauthorized release of information that the individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure. In the context of a research protocol, "confidentiality" refers to the understanding between the participant and investigator (e.g., as set forth in the consent and authorization documents) as to how participant information will be handled, managed, and disseminated (e.g., shared with others) as part of the research.

Private Information means individually identifiable information:

- About behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place
- Which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., a medical record)

Sensitive Information is private information relating, but not limited, to:

- Sexual attitudes, preferences, or practices
- Substance use disorder or treatment (e.g., alcohol, drugs, or other addictive products)
- Illegal conduct
- Information which if released could reasonably cause stigmatization or discrimination or result in damage to areas such as financial well-being, employability, educational advancement, or reputation
- Certain health information, including testing for or diagnosis of certain communicable diseases or psychological or mental health

Confidentiality refers to maintenance of the Researcher's agreement with the participant about how the participant's identifiable private information will be handled, managed, and disseminated.

Geisinger has established the following written policies, together with the other policies referenced in this section, to protect the privacy of research participants and confidentiality of data.

- To approve research (HHS - 45 CFR 46.111(a)(7) and FDA - 21 CFR 56.111(a)(7)), the IRB must determine thee research plan includes adequate provisions to protect the privacy of participants and confidentiality of data.
- To determine research meets criteria for exemption under Exemption categories 2(iii) and 3(i)(C) at 45 CFR 46.104, an IRB member must conduct a "limited review" and be satisfied that, "when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data" (45 CFR 46.111(a)(7)).

Investigators must design studies to maximize confidentiality to avoid unintentional and unauthorized release or other disclosures of data**.** The PI must describe the provisions to protect the confidentiality of data in the study submission. The IRB assesses the information provided in the study submission during the review process. The IRB may ask for additional details during its review, depending on the sensitivity of the information being used, maintained, or disclosed. The greater the sensitivity of the information, the more stringent the security measures needed.

In reviewing confidentiality protections, the IRB considers the nature, probability, and magnitude of harms that would be likely to result from an unauthorized release of the collected information. The IRB evaluates the proposed anonymizing techniques, (e.g., de-identification, coding, data broker), storage plans, access restrictions, data security methods (e.g., encryption) and other relevant factors in making its final determination concerning the appropriateness and adequacy of confidentiality protections.

For active protocols, any changes in confidentiality protection measures must submitted to the IRB via an amendment/modification form, and described in the form, revised study submission, and/or revised protocol. Such changes are reviewed according to the requirements described above for new protocols. The IRB requires that investigators use best practices and adhere to Geisinger security policies to protect the confidentiality of the information collected under a protocol.

Geisinger requires and provides appropriate security measures on all devices and networks. Geisinger has guidelines for best practices for maintaining confidentiality. Geisinger HIPAA Privacy policies include requirements and best practices for:

- Protecting PHI against public viewing.
- Storage and disposal of printed and electronic documents that contain PHI.
- Safeguarding computer workstations and databases that access PHI.
- Disclosing PHI outside of Geisinger

Geisinger Information Security Office (ISO), in collaboration with Privacy Office and IT Compliance, perform Security, Compliance, Privacy (SCP) risk assessments for transmission of identifiable data for research purposes. Any human research study that includes transmission of identifiable data must be submitted and

reviewed via the SCP process prior to protocol submission to the IRB. The SCP assessment and review outcome is submitted to the IRB. IRB staff consult with the Geisinger's Privacy Office or Information Security Office (ISO) as needed to ensure adequate confidentiality protections are in place for the proposed research.

Certificates of Confidentiality (CoC)

CoCs protect the privacy of research subjects by prohibiting disclosure of identifiable, sensitive research information to anyone not connected to the research except when the subject consents or in a few other specific situations. NIH funded researchers are automatically issued a CoC through their award. Other Department of Health and Human Services (HHS) agencies issue CoCs to researchers they fund. Researchers not funded by HHS can apply to NIH or the FDA as appropriate to request a CoC for HHS-mission relevant research.

NIH considers research in which identifiable, sensitive information is collected or used, to include:

- Human subjects research as defined in the Federal Policy for the Protection of Human Subjects (45 CFR 46), including exempt research except for human subjects research that is determined to be exempt from all or some of the requirements of 45 CFR 46 if the information obtained is recorded in such a manner that human subjects cannot be identified or the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
- Research involving the collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual.
    - Research that involves the generation of individual level, human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained as defined in the Federal Policy for the Protection of Human Subjects (45 CFR 46); or
    - Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual, as defined in subsection 301(d) of the Public Health Service Act.

When the PI obtains a CoC, the IRB requires that participants be informed about the protections and limitations under the CoC, through the consent document or HIPAA authorization. The consent document must explain if the investigators will release information under any anticipated mandatory reporting or for internal or external audit purposes (e.g., Geisinger units, DHHS, or FDA). In order that a participant may weigh the risk of such release of information and not expect more confidentiality protection than is provided by the CoC, the IRB requires that the possibility of release for those purposes be stated clearly and explicitly in both the protocol and the consent form. The IRB also requires that any participant enrolled after expiration or termination of a CoC be informed that its protection will not apply to them, and that issuance of a CoC is not an endorsement of the research by the DHHS.

For additional information about CoCs, PIs may consult with IRB staff and visit the NIH Certificates of Confidentiality website.

Confidentiality Protections – During Data Analysis, Dissemination and Retention
Non-exempt human subjects research conducted at Geisinger uses combined informed consent/HIPAA authorization, which requires the PI to securely maintain and store signed documents for a minimum of six years after completion of the study. PIs conducting research through Geisinger must also comply with Geisinger Guidance - Retention of and Access to Research Data and should refer to this guidance when considering the disposal of identifiable data and/or specimens.

Investigators may consider taking additional precautions that were not feasible while the protocol was active, including:

- Removing some or all direct identifiers (e.g., name, medical record number) and coding the information.
- Using qualified data brokers.
- Limiting the individuals who have access to the participant identifiable information.
- Employing and/or contracting secure archival methods or long-term storage services.

The HIPAA privacy regulations continue to apply to any PHI held for research purposes, even after the protocol has been closed.

11.3 HIPAA - Health Insurance Portability and Accountability Act Regulations

DEFINITIONS:

Protected Health Information (PHI) is defined in HIPAA privacy regulations (45 CFR 164) and Geisinger HIPAA policies.
PHI includes all individually identifiable health information (including information in research databases and tissue bank samples with identifiers) relating to the:

- Past, present, or future physical or mental condition of an individual
- Provision of health care to an individual
- Past, present, or future payment for the provision of health care to an individual

Health information is individually identifiable if it contains any of the following:

- Names (Initials)
- Geographic subdivisions smaller than a state
- Dates (except year) directly related to an individual, including birth date, health care service admission or discharge dates, date of death, and all ages over 89 and all elements of dates (including year) indicative of such age, unless aggregated into a single category of ages over 89
- Telephone numbers
- Fax numbers
- E-mail addresses
- Social security numbers
- Medical record numbers

- Health plan beneficiary numbers
- Account numbers
- Certificate/Driver's license numbers
- Vehicle identifiers and serial numbers, including license plate numbers
- Device identifiers and serial numbers
- Web Universal Resource Locators (URLs)
- Internet Protocol (IP) address numbers
- Biometric identifiers, including finger and voice prints
- Full face photographic images and any comparable images
- Any other unique identifying number, characteristic or code

Electronic protected health information (ePHI): PHI that is either transmitted by electronic media or maintained in electronic media.
In accordance with HIPAA regulations [45 CFR 160 and 45 CFR 164], Geisinger IRB serves as the Privacy Board and oversees compliance with those requirements for research purposes on behalf of Geisinger. This is in addition to any requirements under the Common Rule and FDA regulations. Geisinger has established written policies and procedures to implement the HIPAA regulations. Geisinger HIPAA-related policies comply with HIPAA privacy regulations, and the HRPP is responsible for Geisinger policies specific to research:

- *Research Administrative Procedure for Sharing Data*
- Administrative Procedure for Protection of Information in Reviews Preparatory to Research

The IRB, PIs, and other investigators accessing, using, or maintaining PHI have certain duties and responsibilities under those policies and HIPAA, particularly for research activities.

HIPAA Coordination
Geisinger Privacy Office is led by the Chief Privacy Officer and coordinates HIPAA activities throughout the system. Geisinger IRB leadership partners with Geisinger Privacy Office and Legal Services to:

- Navigate complex scenarios for the research use and disclosure of patient data
- Work with investigators to develop compliant paths within their research plans for using and sharing patient data
- Educate investigators and study staff about use and disclosure requirements for the use of patient data, particularly PHI
- Develop guidance for research the use and disclosure of highly protected PHI to ensure compliance with more restrictive Pennsylvania laws and federal laws
- Develop IRB Outcome letter language specific to use and disclosure of HPHI to further educate investigators about what is permitted and their responsibilities for protecting the confidentiality of HPHI

11.4 Highly Protected Health Information

*Geisinger has and follows written policies and procedures that identify applicable laws in the localities where it conducts human research, takes them into account in the review and conduct of research, and resolves differences between federal or national law and local laws. (**AAHRPP Element I.1.G**)*

Highly protected health information (HPHI) is defined by Geisinger Institutional Policy as PHI that is protected by federal or state laws that are more restrictive than HIPAA. Collectively this information is referred to as HPHI. At Geisinger, the following types of information are considered HPHI.

- Mental health records subject to *The Pennsylvania Mental Health Procedures Act [50 P.S. § 7103* and *55 Pa. Code § 5100.36(c)]*
- HIV-related information subject to Pennsylvania's *Confidentiality of HIV-Related information Act (35 PS 7601 et seq.)*
- Substance use disorder records subject to *Pennsylvania Drug and Alcohol Abuse Control Act – Confidentiality of Records (71 PS 1690 et seq.)*
- Federally-supported Medication Assisted Treatment (MAT) program substance use disorder treatment records subject to Federal Law – *Confidentiality of Substance Use Disorder Patient Records* (42 CFR Part 2)

Geisinger IRB, under the direction of the Geisinger Privacy Office and Legal Services, has developed research specific guidance to aid researchers in understanding the necessary requirements for using and disclosing HPHI for research purposes. This guidance (*Geisinger Guidance for Research Use and Disclosure of HPHI)* is for internal use only and is only available on the internal Geisinger IRB SharePoint website. The main IRB study applications incorporate questions to collect information about the use and disclosure of any HPHI in a research study. GIRB uses this information to determine all uses and disclosures are compliant with the applicable governing federal and/or state laws. GIRB seeks guidance from the Geisinger Privacy Office and Legal Services whenever requiring assistance to ensure that intended uses and disclosures are acceptable.

IRB outcome letters clearly document any HPHI that is approved for use and, if applicable, disclosure within each research study. The outcome letters also clearly document the identifiability of the HPHI approved for use and disclosure (fully identifiable, limited data set or de-identified).

As a required condition of federal regulation, *Confidentiality of Substance use Disorder Patient Records* (42 CFR Part 2), all research using and/or disclosing substance use treatment records maintained in connection with any federally assisted Medication Assisted Treatment (MAT) Program requires specific determinations form the individual designated as the "Part 2 Program Director" (42 CFR Part 2.52). The IRB facilitates the required determinations from the appropriate authority in conjunction with the IRB review process when the research requires using and/or disclosing records from either the Geisinger Medication Assisted Treatment Program or Marworth.

11.5 Confidentiality Breach - Unauthorized Release of Information

The IRB requires that PIs immediately inform Geisinger System Privacy Office of any possible or actual unauthorized release of information. The IRB also may receive a complaint or allegation from a participant about such a release. The IRB treats such a release or allegation of release as possible non-compliance.

Potential Violation of HIPAA

If a potential violation in a research study involves PHI, Geisinger also treats it as a potential violation of HIPAA policies and the HIPAA privacy and security regulations. Wrongful uses or disclosures of PHI follow the reporting requirements of Geisinger Policy, *Breach Identification and Risk Assessment*.

Section 12 - Informed Consent and Assent

12.1 Requirements for Informed Consent

*The IRB has and follows written policies and procedures to evaluate the consent process and to require that the Researcher appropriately document the consent process. (**AAHRPPElementII.3.F**)*

Legally effective informed consent must be obtained from participants or their parent(s), guardian, or legally authorized representative (LAR) as a condition for protocol approval, unless the PI requests and received approval from the IRB for waiver of informed consent. All relevant requirements in OHRP in 45CFR 46.111 and 46.116 and in the FDA regulations in 21 CFR 50.20, 50.25, 50.27 and 56.111 that are applicable to the consent process and the consent document must be satisfied in the submission to the IRB. The investigator provides specific details for obtaining and documenting consent in the study submission that is reviewed and approved by the IRB.

Informed consent is a continuing process whereby the investigator and/or members of the study team and research participant have an on-going dialogue about all aspects of a research study that might inform a participant's decisions to take part in the study and to continue his/her involvement as a participant. The purpose of the consent process is to ensure knowledgeable decision-making and voluntary participation.

This process includes:

1. Description of the research study to potential participants.
2. Presentation and explanation of the study activities to the participant.
3. Documentation of the informed consent via a signed and dated written consent document.
4. Ongoing discussions between the investigator and/or members of the study team and the participant regarding matters related to continued participation in the study.

The consent process and document must:

1. Provide sufficient opportunity for the participant; to consider whether to participate.
2. Minimize the possibility of coercion or undue influence.
3. Be free of exculpatory language; and
4. Be in language understandable to the participant or his/her representative.

The IRB also requires that the circumstances of the consent process be culturally and linguistically appropriate for the intended participants.

When participants withdraw from a clinical trial, IRB determines:

- When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remains part of the study database and may not be removed. The consent document cannot give the participant the option of having data removed.
- A researcher may ask a participant who is withdrawing whether the participant wishes to provide continued follow-up and further data collection after their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the participant distinguishes between study- related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non- invasive chart review and address the maintenance of privacy and confidentiality of the participant's information.
    - The researcher must obtain the participant's consent for this limited participation in the study (assuming such a situation was not described in the original consent document). The IRB must approve the consent document.
    - If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the researcher must not access for purposes related to the study the participant's medical record or other confidential records requiring the participant's consent. However, a researcher may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.

IRB Evaluation of Compliance with Informed Consent Requirements

The Investigator submits informed consent documents or requests a waiver or alteration in the consent process for review by the IRB. The IRB reviews the description of the proposed consent process and documentation to ensure that:

1. The informed consent document is consistent with the protocol and other study documents (e.g., investigator's brochure) regarding the purpose, risks, and benefits of the research.
2. The document contains the required and applicable additional elements of informed consent as defined in 45 CFR 46.116 and 21 CFR 50.25.
3. The document minimizes the use of scientific language and contains the appropriate statements regarding safety and effectiveness for FDA regulated research.
4. The circumstances of the consent process minimize the possibility of coercion or undue influence.
5. The information is presented in language understandable to the subject or representative.
6. The consent document must not contain any exculpatory language.

In addition, compliance is evaluated by:

1. Consent form reviews comparing signed and dated consent forms with the IRB-approved versions, when requested as part of a random or for cause audit of the research.
2. Observation of the consent process performed either as a periodic review function of the ORC staff, or as requested by the IRB. *(*See *Section 12.7- Observation of the Consent Process).*

Elements of Informed Consent

Unless a waiver or alteration of consent is granted by the IRB, the Investigator and IRB ensure that informed consent documents include the eight basic required elements and, if appropriate, the six additional elements of consent specified in 45 CFR 46.116 and 21 CFR 50.25.

Informed consent requirements are also found in Geisinger Guidance – Informed Consent & HIPAA Authorization – Required Elements.

Geisinger requirements for informed consent include the following:
Basic Elements of Informed Consent:

- A statement that the study involves research.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of benefits to the subject or others that may be reasonably expected from the research.
- The disclosure of appropriate alternative procedures or course of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent to which confidentiality of records identifying the subject will be maintained.
- For medical research involving more than minimal risk, an explanation as to whether any compensation or any medical treatments are available if injury occurs during study participation.
- The identification of an individual who can be contacted by the subject for answers to questions related to the research, research-related injury, or their rights as a research subject.
- 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 s/he is otherwise entitled.

Additional elements of informed consent (45 CFR 46.116 (b) or 21 CFR 50.25(b)), if appropriate for this study:

- A statement that the 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.
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- Any additional costs to the subject that may result from participation in the research.
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- A statement that significant new findings developed during the research which may relate to the subject's willingness to continue participation will be provided to the subject.
- The approximate number of subjects involved in the study.
- Genetic Information Nondiscrimination Act of 2008 (GINA) language if the study includes genetic testing
- Clinicaltrials.gov language if the study is an applicable clinical trial (LINK TO GUIDANCE)
- COC (Certificate of Confidentiality) language, if the study has a COC or meets NIH criteria for automatically granting a COC

Additional elements of informed consent (45 CFR 46.116(c)) if the study collects identifiable private information or biospecimens (required for informed consents approved on or after May 1, 2018):

- 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 LAR, if this might be a possibility - OR –
    - 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
- 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
- Statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
- For research involving biospecimens, whether the research will (if known) or might include whole genome or exome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen)

Informed consents approved on or after May 1, 2018, should begin with a clear, concise explanation of Key Information to assist a reasonable person in deciding about whether to participate in the research. The following points and order are recommended:

- Statement that the project is research and participation is voluntary
- A summary of the research, including purpose, duration, and list of key activities
- Reasonable, foreseeable risks or discomforts
- Reasonable, expected benefits
- Alternatives, if any

Readability statistics and format of the informed consent should comply with Geisinger standards, considering the population to be studied. Exceptions to these requirements are considered if understandability is deemed reasonable by the IRB.

- Flesch-Kincaid Grade Level = 6-8
- Flesch Reading Ease > 60
- Font = Arial 14
- Spacing = multiple @ 1.15

Additional informed consent requirements for vulnerable and other special populations are addressed in *Section 12.2*.

*Geisinger has and follows written policies and procedures that identify applicable laws in the localities where it conducts human research, takes them into account in the review and conduct of research, and resolves differences between federal or national law and local laws. (**AAHRPP I.1.G**)*

Additional Consent Requirements

IRB consults with the Legal Services to assist investigators and the IRB in understanding, applying, and resolving any conflicts among applicable laws.

In addition to the required and optional elements of consent required by federal research regulations, other information may be required within the consent related to federal, state, and local law. The following topic-specific information must be included in the consent document when applicable to the research.

Health Insurance Portability and Accountability Act (HIPAA)
If the protocol involves protected health information (PHI) as defined by HIPAA, then HIPAA authorization may be included in the consent process. HIPAA authorization is an authorization to use or disclose PHI and must be signed and dated by the subject unless the IRB grants an alteration of HIPAA authorization, allowing verbal authorization.

Combination Informed Consent/HIPAA Authorization templates are provided on the HRPP website.

If the ICF includes HIPAA authorization (or if stand-alone authorization is used, the following elements are required (See also *Geisinger Guidance – Informed Consent & HIPAA Authorization – Required Elements*):

- A specific/meaningful description of PHI that will be collected for research and the purpose of collecting this information (e.g., *for this research*)
- The person or class of persons who may use or disclose the PHI collected for research (e.g., *study doctor and study staff*)
- The person or class of persons to whom PHI collected for research may be disclosed and the purpose of such disclosure (e.g., *We will share your information with the study sponsor and its partners for this research*)
- Potential for disclosed PHI to be redisclosed by the recipient and no longer protected by Privacy Rule (e.g., *Geisinger is required by law to protect your health information. Some laws that protect your health information only apply to hospitals, doctors' offices, and other healthcare providers. When your information is shared outside of Geisinger, some federal privacy laws might not apply.)*
- The expiration date of the authorization (e.g., *may use or use and share your health information until the end of study* or … *indefinitely for this study's purpose*)
- Consequences to the individual of a refusal to sign the authorization (e.g., *cannot take part in the study/receive research-related treatment* (if applicable) *without signing consent/authorization)*
- The individual's right to revoke authorization, process to revoke and consequences of such revocation (e.g., *By signing this form, you are giving Geisinger permission to use and share your health information indefinitely. If you change your mind, tell us in writing to stop using and sharing your information. Write to: [Enter name of study, internal zip code and address] Information already collected will still be used. We will only use and share new information if it is needed to protect your safety or follow with the law.*)
- Participant or LAR signature and date

HIV Testing
Federal and state regulations outline certain requirements for HIV testing. If the research protocol includes testing for HIV, separate clinical HIV testing consent processes must be followed in accordance with PA Act 148 and Geisinger Policy – HIV Testing Protocol.

- "CONFIDENTIALITY OF HIV-RELATED INFORMATION ACT" Act of 1990, P.L. 585, No. 148
- Act of Jul. 7, 2011,P.L. 274, No. 59 Cl. 35 - CONFIDENTIALITY OF HIV - RELATED INFORMATION ACT - LEGISLATIVE INTENT, CONSENT TO HIV - RELATED TESTS AND COUNSELING (state.pa.us)

HIV Results – Use & Disclosure

PA Act 148 defines *"Confidential HIV-related information"* as any information that is in the possession of a person who provides one or more health or social services or who obtains the information pursuant to release of confidential HIV-related information and which concerns whether an individual has been the subject of an HIV-related test, or has HIV, HIV-related disease or AIDS; or any information that identifies or reasonably could identify an individual as having one or more of these conditions, including information pertaining to the individual's contacts.

Pennsylvania's Act 148 prohibits health-care providers and social service providers from disclosing identifiable HIV-related information without the permission of the subject, except in certain limited instances. If the research includes use and disclosure of identifiable confidential HIV- related information, the consent/authorization must include the following information (35 P.S. §7607(c)):

- Name or general designation of the person permitted to disclose (e.g., study doctor)
- Name/title of individual or name of organization to which the information is disclosed
- Purpose of the disclosure (e.g., research study)
- How much/what kind of information is to be disclosed
- Name and signature of the subject
- Date on which the consent form was signed
- A statement that consent may be withdrawn at any time, except for disclosure of information already sent
- Date/event/condition of expiration of consent, if not revoked earlier

The use and disclosure of de-identified confidential HIV-related information for research is not prohibited.

Genetic Testing

If a protocol includes genetic testing, the IRB requires that the informed consent disclose the risks specific to this type of testing, including protections and limitations of the Genetic Information Nondiscrimination Act of 2008 (GINA). If research might include whole genome sequencing (WGS) or whole exome sequencing (WES), this must be explained in the informed consent.

Data and Tissue Repositories

NIH guidance on Data and Tissue Repositories is of interest to investigators who collect subjects' data or tissues for repositories, and IRB staff and members who review such protocols.

When such repositories collect individually identifiable health information of participants, the HIPAA privacy regulations in 45 CFR Parts 160 and 164 must also be satisfied. This may require either a written HIPAA authorization from the participants or a waiver of authorization by the IRB. These requirements are discussed in Section 11.

Genome-Wide Association Studies (GWAS)

GWAS examine genetic variation across the entire human genome and are designed to identify genetic associations with observable traits or the presence or absence of a disease or condition. Genomic research advances our understanding of factors that influence health and disease, and sharing genomic data provides opportunities to accelerate that research through the power of combining large and information-rich datasets. To promote robust sharing of human and non- human data from a wide range of genomic research and to provide appropriate protections for research involving human data, the National Institutes of Health (NIH) issued the NIH Genomic Data Sharing Policy (GDS Policy) on August 27, 2014 in the NIH Guide Grants and Contracts, and in the Federal Register on August 28, 2014. The GDS Policy and related documents are available at:

- GDS Policy PDF
- Preamble to the GDS Policy
- Supplemental Information to the GDS Policy
- NIH Press Release on the GDS Policy
- NIH Guide Notice on Implementation of the GDS Policy for NIH Grant Applications and Awards
- NIH Guide Notice on Development of Data Sharing Policy for Sequence and Related Genomic Data

GWAS - Institutional Certification and IRB Review

Under the **NIH's Policy for Sharing Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS),** the Institutional Official and IRB are responsible for certifying that plans for the submission of genotype and phenotype data from GWAS to the NIH meet the requirements of the policy.

Certification by Geisinger's IO should include:

- The data submission is consistent with all applicable laws and regulations, as well as institutional policies.
- The appropriate research uses of the data and the uses that are specifically excluded by the informed consent documents are delineated.
- The identities of research participants will not be disclosed to the NIH GWAS data repository, and
- IRB reviewed the investigator's proposal for data submission and verified that:
    - The protocol for collection of genotype and phenotype data to be submitted to the NIH GWAS repository was consistent with the 45 CFR 46.
    - The submission of genotype and phenotype data to the NIH GWAS data repository and subsequent sharing for research purposes are consistent with the informed consent of study participants from who the data were obtained.
    - It has considered the risks to individuals, their families, and groups or populations associated with data submitted to the NIH GWAS data repository.
    - The investigator's plan for de-identifying datasets is consistent with the standards outlined in the NIH GWAS policy.
- After review of the study submission, the IRB may find the consent documents do not meet the criteria listed above. The IRB may either:
    - Decide that it is appropriate and necessary for the PI to seek explicit consent of the research subjects for submission to the NIH GWAS repository and subsequent sharing; or they may
    - Determine that re-consent is not feasible or appropriate for a given study.

- The IRB may also determine that it cannot verify that one or more of the other above required criteria have been met for submission to the NIH GWAS repository.
- In all these cases, the investigator's data-sharing plan should explain the reasons the IRB determined that submission to the GWAS repository was considered inappropriate.

The Principal Investigator (PI) is responsible for ensuring that the data submitted for inclusion in the GWAS data repository is appropriately coded or de-identified.

Data sharing plans should describe how the requirements of this policy will be met:

- Submission of data to the NIH GWAS repository and subsequent sharing of data must be consistent with the informed consent document
- How informed consent will be obtained for prospective data and samples
- How data will be de-identified for submission to the GWAS repository

GWAS - Informed Consent

Prospective Studies

The informed consent process and document should make clear that participants' DNA will undergo genome-wide analysis and the resultant genotype and phenotype data will be shared with the NIH GWAS data repository for research purposes.

Retrospective Studies

The IRB must determine whether the informed consent document, under which existing genetic materials and data were obtained, is consistent with the submission of data to the NIH GWAS repository and the sharing of that data in accord with the GWAS policy.

For studies that propose to use existing data or specimens, the IRB may determine that the signed consent document is not consistent with submission to the GWAS repository and decide that it is necessary to seek explicit consent of the research subjects for submission to NIH GWAS repository and subsequent sharing.

The criteria for waiver of consent in 45 CFR 46 are not applicable when data or specimens will be submitted to NIH GWAS repository. The IRB must apply criteria outlined in the NIH GWAS policy when making its determination.

Consent Templates and Glossary of Lay Terms

The HRPP website provides consent form templates, parental permission and assent templates for research involving children.

To assist PIs in preparing consent documents comprehensible to lay persons (i.e., at approximately an 8th grade level) a Glossary of Lay Terms is also available on the HRPP website.

Short Form Consent Process

Federal regulations permit the use of a short form consent process (45 CFR 46.117) with the prior approval of the IRB. The short form consent is an option available to investigators when few non-English subjects are

expected to enroll in the research. However, the IRB encourages the use of a full consent form translated into the participant's language whenever possible.

The short form consent process may be approved by the IRB, on a protocol-specific basis, for use with participants who are non-English speaking or in other specific circumstances where the participant may understand but have problems signing. The IRB considers the study complexity and the amount and duration of participant involvement when determining if using the short form consent process is appropriate and can be approved.

For use of the short form of consent documentation, the IRB determines that:

- The short form states that the elements of consent required by regulations have been presented orally to the participant.
- **A written summary embodies the basic and appropriate additional elements of consent** unless the IRB approves alteration of consent. The summary must be IRB-approved, and the content must be consistent with the information contained in the informed consent. The summary can be the IRB approved informed consent form used as the written summary of what will be said to the participant
- There will be an impartial witness to the oral presentation. The witness may be the interpreter (including the hospital interpreter), staff, a family member, or other person.
- The witness must attest to the adequacy of the consent process and the participant's voluntary consent.
- For participants who do not speak English, the witness will be conversant in both English and the language of the participant.
- The participant will sign and date the short form.
- The witness will sign and date both the short form and a copy of the summary.
- The person obtaining consent will sign and date a copy of the summary.
- A copy of the summary and the signed and dated short form will be given to the participant.

See Guidance – Short Form Consent Process for information on the requirements for using the short form consent. Geisinger IRB has also approved the following short form consent documents for investigators' use, which are posted on the HRPP website. These represent the most prevalent languages of the Geisinger patient population:

- *Short Form Consent – English Translation*
- *Short Form Consent – Spanish*
- *Short Form Consent – Arabic*
- *Short Form Consent – Bulgarian*
- *Short Form Consent – Mandarine-Chinese Simplified*
- *Short Form Consent – Nepali*
- *Short Form Consent – Russian*
- *Short Form Consent – Vietnamese*

Electronic Consent Process

Unless the IRB waives the requirement for the investigator to obtain a signed consent or permission form based on the HHS regulations 45 CFR46.117, a written consent or permission form, which may be an electronic version, must be given to and signed by the subject or the subjects' LAR or the parents of

subjects who are children. Some form of the consent document must be made available to the subjects or the parents of subjects who are children in a format that they can understand and retain. OHRP allows electronic signature of the document if such signatures are legally valid.

The IRB must consider:

- How is the electronic signature being created?
- Can the signature be shown to be legitimate?
- Can the consent or permission document be produced in a hard copy for review by the subject?
- Is the system being used secure for electronic authentication that provides an encrypted identifiable "signature"?
- Does the technology being used ensure safeguards of protection of privacy and confidentiality?

Posting of Clinical Trial Consent Form on Publicly Available Web Site

For each clinical trial approved by the IRB on or after January 21, 2019, one IRB-approved informed consent form used to enroll subjects must be posted by the primary awardee or the Federal department or agency component conducting the trial on a publicly available Federal Web site that will be established as a repository for such informed consent forms. If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal Web site (*e.g.,* confidential commercial information), such Federal department or agency may permit or require redactions to the information posted. The informed consent form must be posted on the Federal Web site after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol. (See 45 CFR 46.116.)

12.2 Consent Procedures for Vulnerable and Other Special Populations Including Consent by a LAR

*The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question. (**AAHRPP Element II.4.B**)*

When considering approval of research, the IRB considers issues such as the selection of participants, privacy and confidentiality, coercion and undue influence, and risk-benefit analysis. Decisions are guided by the ethical principles underlying human research as set forth in the Belmont Report. Special consideration is given to protecting the welfare of vulnerable participants, such as children, pregnant women, fetuses, persons with impaired decision-making, or economically or educationally disadvantaged persons (45 CFR 46.111(b) and 21 CFR 56.111(b)). There are specific regulatory provisions and considerations for providing legally effective informed consent for research in such populations.

Adults with Impaired Decision-Making Capacity

*The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question. (**AAHRPP Element II.4.B**) (Also addresses portions of **AAHRPP Element II.4.A**)*

If an adult meets the legal requirement for competence, then they must consent to their own participation in the research. The November 30, 2006 PA Act 169 on Advanced Directives defines which adults are competent to consent to treatment and which are incompetent. Individuals who are competent to make their own treatment decisions have the capacity to consent to research.

However, many individuals who lack the competence to consent to treatment still retain the capacity to consent to research. For example, an adult with diminished capacity may lack the ability to manage the complexity of their required healthcare; yet they might have the ability to understand the purpose, procedures, and other elements of consent for a minimal risk research study, such as one involving a blood draw or survey. That said, an individual who has the capacity to consent to participate in a minimal risk study might not have the capacity to comprehend all the components of a randomized clinical trial. They might, however, be able to understand enough to assent to their own participation after their legally authorized representative (LAR) grants permission for them to take part.

Legally Authorized Representative (LAR) – 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. 21CFR50.3 (l); 28 CFR46.102 (c) & 45 CFR46.102.

Under PA Act 169, incompetent means a condition in which an individual, despite being provided appropriate medical information, communication supports, and technical assistance, is unable to:

- Understand the potential benefits, risks and alternatives involved in a specific proposed health care decision.
- Make the health care decision on his own behalf; or
- Communicate that health care decision to any other person.

PA Act 169 states that these findings must be documented in the electronic health record. The term is intended to permit individuals to be found incompetent to make some health care decisions, but competent to make others. When an adult does not have the capacity to consent to participate in the research, they cannot take part without the consent of their legally authorized representative (LAR). If planning to enroll participants with diminished capacity, the investigator must develop a plan to determine whether the prospective adult participant has the capacity to consent and if they do not, whether there is a LAR who can consent on the adult's behalf. In Pennsylvania, a competent adult may designate an individual of their choice to serve as their LAR.

Examples include:

- If that individual loses the ability to consent due to a temporary situation (surgery, trauma), their LAR may act on their behalf.
- Someone with a progressive condition, such as Alzheimer's, can also designate an LAR before they lose the competence to consent.
- Adults with diminished capacity due to neurological impairment (e.g., genetic, congenital, traumatic) who have transitioned from childhood to adulthood.

The issue as to who can be an LAR is determined by the laws of the area in which the research is conducted (e.g., local or state law). Most states, including Pennsylvania, do not have laws specifically addressing the issue of consent in research. In Pennsylvania, the laws that address who are authorized to give consent on behalf of another person to specific medical procedures or to medical treatment may be relevant if the research involves medical procedures or medical treatment. OHRP Guidance states that "When the laws of the jurisdiction in which the research is being conducted provide a reasonable basis for authorizing an individual to consent on behalf of a prospective subject to their participation in the research procedures(s), OHRP would consider such an individual to be an LAR as defined by HHS regulations at 45 CFR 46.102."

The following, in descending order of legal authority, can serve as an individual's LAR and provide consent for research purposes:

- A duly appointed court guardian from a competent jurisdiction authorizing the guardian to make medical decisions on behalf of the patient.
- A properly notarized durable power of attorney appointing that person for purposes of medical decision-making.
- State law usually establishes the priority order of individuals who may serve as the LAR in situations where the incompetent individual does not have a court appointed guardian, durable power of attorney or designated LAR. In Pennsylvania, for example, PA Act 169 dictates the following order:
    - Spouse
    - Adult child
    - Parent
    - Adult sibling
    - Adult grandchild
    - Close friend (refer to Consent by Legally Authorized Representative (LAR) – Affidavit if documentation of the ability to serve as LAR is not available)
        - If a close friend is used as the LAR, that person should present an "Affidavit" stating he/she (i) is a close friend of the study participant, (ii) is willing and able to become involved in the research study participant's health care, and (iii) has maintained such regular contact with the study participant to be familiar with the study participant's activities, health and religious and moral beliefs.

If there is more than one LAR in the highest priority and the LARs disagree and there is no majority, the study participant cannot be enrolled in the study. Investigators are encouraged to consult the Geisinger Department of Legal Services and Geisinger Bioethics Committee in these situations.

DEFINITIONS:

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

Guardian is a fiduciary who has care and management of the estate or person of a minor or incapacitated person. 20 Pa. C.S.A. § 102. An individual who is authorized under applicable state or local law to consent

on behalf of a child to general medical care when the general medical care involves participation in research. Individual authorized to consent on behalf of a child to participate in research. 21 CFR50.3(s).

Use of LAR

In instances where the investigator reasonably believes that enrollment of certain patients may involve the use of LAR, the study submission should include the following information to establish the rationale for the use of surrogate consent:

- A description of the subject population under study.
- A description of the proposed research study subset that needs LAR and the reason why use of LAR is necessary.
- A description of benefits the study participant may expect from the research study.

IRB Review

Based on the research proposal submitted to the IRB, the IRB must consider and evaluate the following criteria before approving research involving adult participants with impaired decision- making capacity:

- Equitable selection of subjects, particularly given the special considerations posed by research involving vulnerable populations.
- Favorable risk/benefit assessment and whether the research is of importance to the vulnerable population.
- Ability of the individual to give legally effective informed consent and if not, should they be involved in the discussion of the research with the LAR.
- Adequacy of the investigator's plan for assessing the research subject's capacity to provide consent (*See Guidance – Assessment and Determination of Incompetence*);
- Provision for LAR consent process for every participant with limited decision-making capacity (45CFR 46.116 and 21 CFR 50.20) that is consistent with Geisinger's policies, procedures and guidance for consenting individuals with diminished decision-making capacity;
- Appropriateness and adequacy of investigator's plan to obtain assent of the participants.
- Potential pressures on the subject or subject's LAR to consent or refuse participation.
- Alternatives to participation.
- Enrollment of this population meets all ethical standards and federal requirements.
- Additional protections have been incorporated into the study to provide added protection for individuals with limited autonomy. Based on the level of risk involved in the research and the likelihood that participants will derive benefits from participation, the IRB may consider additional safeguards to protect participants, such as:
    - Requiring the involvement of participant advocates.
    - Requiring independent monitoring.
    - Appointing a monitor to supervise the informed consent process.

The LAR consent process may only be used with prior approval of the IRB after consideration of the criteria listed above. Submissions to the IRB including a LAR consent process and form must include a consent form with Signature Page lines for the following:

- Name of the research participant
- Signature of the research participant and date

- Signature of the legally authorized representative and date.
- Statement as to the authority of the research study participant's LAR or relationship to the research study participant (e.g., court-appointed guardian, spouse).
- Signature of the individual who witnesses the willingness of the LAR to provide consent for the participant (not required in Pennsylvania); and
- Signature of the person conducting the informed consent discussion and date.

Other requirements for obtaining LAR consent on behalf of the research participant:

- Documentation of guardianship order or durable power of attorney appointing a health care agent must be retained in the research study participant's electronic health record and/or research record.
- Consent discussions with the LAR should emphasize the LAR's ability to make a decision that would conform as closely as possible to what the study participant would have done or intended under the circumstances. The LAR should be asked to consider evidence that includes the study participant's personal, philosophical, religious, and moral beliefs and ethical values relative to the purposes of life, sickness, medical procedures, suffering and death. When possible, the LAR should consider how the study participant would have weighed the risks and benefits of the proposed study.
- The LAR may express his/her consent to the person obtaining consent in the presence of one adult witness (at least 18 years of age) not directly involved with the research study, however this is not required in Pennsylvania. The witness should sign the consent form.
- The LAR will have the same right as the study participant to receive information on the research study, the study participant's condition and to withdraw consent for further participation.
- When a LAR provides consent, it is preferable for that LAR to remain the responsible party for all research decisions related to the research study in the future. The LAR should be informed of this.
- If, during a research study where consent had been obtained through the assistance of a legally authorized representative, a study participant regains the capacity to make decisions about participation in a research study and provide consent, the investigator and/or approved designee must assess the continued willingness of the research participant to participate in the research study.
    - The study participant will be made aware of the research study, the identity of the LAR who enrolled them in the research study.
    - The investigator and/or approved designee shall "re-consent" the patient in the study.
    - A new consent form will be completed by the study subject and dated accordingly.
    - Both the original consent form executed by the LAR and the new consent form signed by the study participant should be retained.
    - If the subject chooses not to continue participation in the study, the investigator must honor that decision. The research study participant should be immediately withdrawn, and appropriate documentation should be entered in the research and/or health record to reflect the patient's decision to withdraw from the study.
        - Absent prior submission of research data, the data already collected on this subject may not be used as part of the study data.

Executing Consent on Behalf of Mentally Competent but Physically Unable to Sign Consent

If an individual is determined to be eligible for participation in a particular research study and is mentally competent for purposes of decision-making, but lacks the physical capacity to sign the written consent form, the following procedures should be followed:

5. When a study participant who is physically unable to sign the consent form is identified, study personnel will prepare a "Consent Form Addendum for Patients Unable to Sign the Consent Form."
6. Study personnel will identify two individuals – one of whom can serve as signatory and one can serve as an impartial witness. Both must be unconnected to the study and to the investigators of the study.
7. The consent form will be read by the prospective study participant or alternatively may be read to the prospective study participant by investigator or member of the study team. After this process is complete and the prospective study participant has been given appropriate time to ask questions and raise any other issues, study personnel should leave the room to avoid any appearance of potential coercion or impropriety.
8. In the presence of the witness, the signatory will ask the prospective study participant, if they agree to participate in the research study.
9. If the study participant verbally agrees to participate, the signatory (who questioned the study participant) will next ask if it is acceptable for the signatory to sign the consent form on behalf of the study participant.
10. If the study participant provides permission, in the presence of the witness, the signatory will sign the study participant's name, on the "Study Participant" signature line on the consent form.
11. The signatory will then sign their name on the line provided on the "Consent Form Addendum for Patients Unable to Sign the Consent Form".
12. The witness will sign the "Consent Form Addendum for Patients Unable to Sign the Consent Form" on the line indicated for the witness.
13. In addition to the consent form, the process should be documented in the study participant's electronic health record and/or research record. Documentation of the consent process should include that the study participant was (a) mentally competent to make decisions regarding enrollment in the research study but could not physically execute the consent form; (b) the nature of the impairment that prevented the study participant from executing the consent document; (c) the identity of the signatory and any relationship to the study participant; (d) the identity of the additional witness and any relationship to the study participant.

Pregnant Women, Fetuses and Neonates

The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question. ***(AAHRPP Element II.4.B)***

In accordance with HHS regulations, the IRB requires that additional protections be provided to pregnant women, fetuses and neonates involved in research. General considerations related to research involving pregnant women, fetuses and neonates are detailed in HRPP Handbook Section 9. Additional protections and informed consent requirements are specified in Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research (HHS) and are summarized in Geisinger Guidance - Research Involving Pregnant Women, Fetuses, and Neonates

The IRB determines whether the approval criteria for consent are met when research involves **pregnant women, fetuses, or neonates**. The assigned reviewer determines and documents that:

- The consent of the mother is obtained in accordance with the regulations.
- If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the father is also obtained in accordance with the regulations, except that the father's consent does not need to be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
- Individuals providing consent are fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.

The IRB determines whether the approval criteria for consent and permission are met when research involves **neonates of uncertain viability**. The assigned reviewer determines and documents that:

- Individuals providing consent are fully informed regarding the reasonably foreseeable impact of the research on the neonate.
- The legally effective consent of either parent of the neonate is obtained in accordance with the regulations.
    - If neither parent can consent because of unavailability, incompetence, or temporary incapacity, the legally effective consent of either parent's legally authorized representative is obtained.
    - The consent of the father or his legally authorized representative does not have to be obtained if the pregnancy resulted from rape or incest.

The IRB determines whether the approval criteria for consent and permission are met when research involves **nonviable neonates**. The assigned reviewer determines and documents that:

- Individuals providing consent are fully informed regarding the reasonably foreseeable impact of the research on the neonate. The legally effective consent of both parents of the neonate is obtained in accordance with the regulations.
    - If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the consent of one parent of a nonviable neonate is sufficient, except that the consent of the father does not have to be obtained if the pregnancy resulted from rape or incest.
    - The consent of a legally authorized representative of either or both parents of a nonviable neonate is not allowed.
- The waiver and alteration provisions are not applied.

When it has been determined that the **neonate is viable**, the neonate is considered a **child** and the consent requirements described below apply.

Children and Consenting Minors

*The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question. (**AAHRPP Element II.4.B**)*

The IRB imposes additional protections on research involving children, in accordance with Subpart D – Additional Protections for Children as Subjects in Research (HHS) and Subpart D – Additional Protections for Children as Subjects in Research (FDA).

By regulatory definition, "children" are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. In Pennsylvania, the legal age for consent to treatments or procedures involved in research is 18, but there are important exceptions. These exceptions are outlined in *Geisinger Permissions and Informed Consent Policy*.

Since children cannot legally provide consent, informed consent must be obtained from parents ("parental permission") or the legally appointed guardian. The IRB requires the investigator to obtain the permission of a child's parent(s) or guardian before enrolling the child in a study. See Guidance - Parental Permission.

Parental or Legal Guardian Permission
The IRB must determine that adequate provision have been made for soliciting the permission of each child's parents or legal guardians. Parents or legal guardians must be provided with the required elements of consent, as well as any additional elements of informed consent as the IRB deems necessary. Permission by parents or legal guardians must be documented in accordance with 45 CFR 46.117.

Definitions
Parental Permission: The agreement of parent(s) or guardian to the participation of their child or ward in research.

Guardian**:** An individual or official appointed through a state or local law, a court order, or upon the death of a parent through the parent's will to have custody of a child, either temporarily or permanently, with the associated rights to make decisions on behalf of the child. (Normally, the authority of a parent ceases upon the court appointment of a guardian).
In Pennsylvania, a guardian has the authority to consent on behalf of a child to general medical care (and therefore meets the DHHS and FDA definition of "guardian") when his or her court issued letters of guardianship include the authority to consent on behalf of a child to general medical care.

Ward**:** (defined by FDA) a child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law.

Research Requiring Only One Parent's Permission

- HHS
  - 45 CFR 46.404 - Research not involving greater than minimal risk
  - 45 CFR 46.405 – Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
- FDA
  - 21 CFR 50.51 - Research not involving greater than minimal risk

- 21 CFR 50.52 – Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

If the research into which the child is to be enrolled involves no more than minimal risk or if the research involves greater than minimal risk but presents the prospect of direct benefit to the individual human subject participants, then, if the child is in the legal care/custody of his/her parents, the IRB may find that the permission of only one of the child's parents is sufficient to safeguard the interests of the child.

If the child is not in the legal care/custody of his/her parents, then the child's legal guardian may sign the informed consent/permission documentation provided, however, that if the child is a ward of the state, then a signed statement should be obtained from the legal authorized representative certifying that he/she is the legal authorized representative and copies of appropriate supporting documentation (e.g., copy of court order) also should be obtained and kept with the certification.

Research Requiring Both Parents' Permission

- HHS
  - 45 CFR 46.406 – Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition
  - 45 CFR 46.407 – Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children
- FDA-regulated Research
  - 21 CFR 50.53 – Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition
  - 21 CFR 50.54 – Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

If the research into which the child is to be enrolled is greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition; or if the research is not otherwise approvable but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children, permission from both parents is required (unless one parent is deceased, unknown, incompetent, not reasonably available, or only one parent has legal responsibility for the care/custody of the child).

Research Risk	Required Signatures	HHS/FDA Children's Categories
Minimal risk	One parent/guardian	45CFR 46.404 / 21CFR50.51
More than minimal risk / direct prospect of benefits to child	One parent/guardian	45CFR 46.405 / 21CFR50.52

More than minimal risk / NO direct prospect of benefits to child	Two parents/guardians	45CFR 46.406 / 21CFR50.53 45CFR 46.407 / 21CFR50.54

Waiver of Parental Permission
The IRB may waive the requirement for obtaining the permission of a parent/legal guardian if:

- The research meets the requirements for waiver set forth in 45 CFR 46.116; or
- The IRB determines that the protocol is designed for conditions or a subject population for which permission from a parent or legal guardian is not a reasonable requirement to protect the subjects (e.g., neglected or abused children) AND an appropriate mechanism for protecting the children who participate is substituted, and further if the waiver is not inconsistent with federal, state or local law.

NOTE: The choice of an appropriate substitute mechanism will depend upon the nature and the purpose of the research activities, the risk and anticipated benefit to the subjects, and the subjects' age, maturity, status, and condition.

Documentation in IRB Records of Parental Permission Requirements
The IRB shall document its determination of whether permission must be obtained from one or both parents in the IRB meeting minutes (for convened meeting review), specific study records (for expedited review), and in the approval letter to the PI.

Assent from Children
When, in the judgment of the IRB (after reviewing information provided by the PI), children can provide assent, the IRB may determine that assent is required, that adequate provisions are made for soliciting the assent of the children, and whether and how assent must be documented. Children aged seven and above may be asked to give assent to participate.

Definitions
Children: [DHHS and FDA] 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. Subpart D of the DHHS and/or FDA must be applied only if an individual involved in the research meets this definition.
In Pennsylvania, the legal age for consent to treatments or procedures involved in research is 18, but there are important exceptions. These exceptions are outlined in *Geisinger Permissions and Informed Consent Policy*.

***Assent*:** A child's affirmative agreement to participate in research. Absent affirmative agreement, mere failure to object is not assent.

Obtaining Assent from Children Under Age 7
The Geisinger IRB presumes that children below the age of 7 years and any children with a cognitive impairment, such that their ability to understand would be like a child less than 7 years old, will not be required to provide assent prior to participation in research if their parent(s) or legal guardian provide(s)

permission for the children to participate in the research. However, children should be engaged in the assent discussion and provided with a description of the research protocol using language and concepts appropriate to the child's developmental ability whenever possible.

From 7 through 14 Years of Age

Unless the Geisinger IRB grants waiver of consent, the IRB requires that children ages 7-14 years old be engaged in the assent discussion and provided with a description of the research protocol using language and concepts appropriate to the child's developmental ability. and that their verbal assent to participate is obtained and documented (i.e., on assent form or in medical and/or research record). The PI may submit an assent script and/or document (i.e., information sheet, video, etc.) to the IRB for review.

From 15 through 17 Years of Age

Children ages 15-17 years old must be provided with a written assent document or script (i.e., information sheet, video, etc.) that explains what will happen, and why, risks involved, any benefits, and the option that they could withdraw. The specific assent details will be determined by the PI for inclusion of the population under study and the child's ability to understand. The child's assent will be obtained prior to enrollment in any research (unless assent is waived by the IRB) or the person obtaining consent indicates why assent could not be obtained. The assent process must be documented (i.e., on assent form or in medical and/or research record). *Protocol specific requirements may dictate that signed assent is obtained, such as, by request of the IRB, PI, or study sponsor.

Age	Assent (Minimal Requirements)	Child's Signature
< 7 years	None	None
7 – 14 years	Verbal, with documentation on Parental Permission/Assent form or in the research or medical record (unless IRB grants waiver of assent)	None
15 – 17 years	Verbal or written, with documentation on Parental Permission/Assent form or in the research or medical record (unless IRB grants waiver of assent)	Yes, (unless IRB grants waiver of documentation of assent)

Although age is used as the primary criteria in determining an appropriate means of obtaining assent, factors such as literacy and cognitive development must also be considered. The need for flexibility in the methods for obtaining assent from children is universally recognized. Because a single method of obtaining assent may not be appropriate for all potential participants, investigators may need to be prepared to use different approaches with different participants.

PIs should ensure that the assent form (document, etc.) is age appropriate and study specific, considering the typical child's experience and level of understanding. The assent form should be written in a format that takes into consideration the age(s), literacy, and cognitive development of the children who may participate in the research. In most studies, 15-17-year-old children might be asked to provide assent using the document that parents and/or adult participants are signing.

The assent description may include essential elements about the research protocol including:

a. a description of why the research is being conducted.
b. a description of what will happen and for how long or how often it will happen.
c. an explanation that it is up to the child to participate, and that the child may refuse to participate.
d. an explanation of whether the procedures in the research will hurt and if so for how long and how often.
e. a description of what other choices the child may have instead of participating in the research.
f. a description of any good things that might happen from the research; and
g. a description of how and of whom the child may ask questions regarding the research.

Geisinger templates/signature pages for parental permission and assent are designed to facilitate the assent process.

Waiver of Assent

In general, a minor who is participating in research should actively show his/her willingness to participate in the research, rather than just complying with directions to participate without resistance. When judging whether children are capable of assent and evaluating the assent process to be used, the IRB shall consider the ages, maturity and psychological state of the children who are involved. The Geisinger IRB has the discretion to judge children's capacity to assent based on the characteristics of the group of children who will be participating in the research, or on an individual basis.

The IRB may determine that the assent of the children is not a necessary condition for proceeding with the research if:

a. the capability of some or all children who will be enrolled is so limited that they cannot reasonably be consulted; or
b. the intervention or the procedures involved in the research hold 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.

Documentation in IRB Records of Assent Requirements

The IRB, as appropriate, shall document the following in meeting minutes for protocols reviewed at a convened meeting review or the specific study record for protocols reviewed by expedited review, whether subjects are capable of assenting; whether assent is or is not required for the research to proceed; if assent is required, whether and how assent must be documented; or if subjects are not capable of assenting, whether assent may be waived and how the protocol meets the requirements for waiver.

Inconsistency Between Parent/Legal Guardian Permission and Child Assent

In general, a child's refusal to assent to participate in a research protocol will override permission granted by the parent/legal guardian for participation. However, the investigator may consider a request to waive assent on an individual subject basis in situations in which the parent/legal guardian has given permission for participation, but the child has refused assent.

When a Child Subject Becomes an Adult – Consent for Continued Participation

Unless the IRB determines that the requirements for obtaining informed consent can be waived, investigators should seek and obtain legally effective informed consent, as described in 45CFR46.116, for the now-adult subject for any ongoing interactions or interventions with the subjects. This is because the prior parental permission and child assent are not equivalent to legally effective informed consent for the now-adult subjects. However, the IRB could approve a waiver of informed consent under 45CFR46.116, if the IRB finds and documents that the required conditions are met.

If the research study involves children (age < 18 years of age) who will continue to undergo research interventions (including collection of identifiable private information) after they become adults, the IRB submission (protocol, application, etc.) should address a mechanism (e.g., addendum informed consent document with copy of originally signed consent form attached; new consent form) whereby direct consent for continued participation in the research study will be obtained from these individuals at the time they reach adult status. If details are not included in the sponsored protocol, then consent must be obtained when the child reaches 18 years of age to allow their continuation in the research study.

For Children's Oncology Group (COG) Studies Only:
The Consent for Continued Participation in COG Research When Participants Turn 18 form is approved to be used for the Pediatric Hematology/ Oncology Department.

When Minors, Including Emancipated Minors, May Consent as Adults

Definitions
Minors: Persons under 18 years of age. Because some minors can consent for themselves to some research procedures, not all "minors" meet the federal criteria for being "children."

Emancipated Minors*:*

a. A minor who is aged 16 or over, who has left the parental household and has established himself as a separate entity free to act upon his own responsibility, and who can act independently of parental control. If the minor again lives with his parents, he will no longer be considered emancipated unless he remains independent of his parents' control.
b. An orphan who is aged 16 or over and who has sufficient mental ability to make a bargain.
c. A minor who is married, regardless of whether the person continues to live in the parental household. If the marriage is terminated by divorce or death of the spouse, the minor is still emancipated. If the marriage is terminated by annulment, the state of emancipation is as though the marriage had never occurred.
d. An unmarried child committed to the care and control of the county authority can become emancipated before the age of 18 only by action of the court.
e. A minor parent or pregnant mother with control over his/her child and is not under the control of his/her parents.

In accordance with Pennsylvania law, there are certain situations in which the IRBs permit minors to consent to participation in research as adults without parental permission. If the PI is not familiar with such laws, he or she may need to consult with IRB staff prior to enrolling a minor in a research study without parental permission, to ensure that the applicable legal requirements are met. The criteria under which a

waiver of parental permission may be granted are discussed in the Guidance Consent for Protocols Involving Children and Consenting Minors.

See Geisinger guidance documents:

- Consent for Protocols Involving Children and Consenting Minors
- Parental Permission
- HRPP Handbook Section 12.4 for information on documentation of informed consent, and assent

Illiterate Participants

*The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question. (**AAHRPP Element II.4.B**)*

The IRB allows individuals who speak and understand English, but who cannot read the consent materials due to illiteracy, to enroll in a study by "making their mark" (e.g., signing or marking an "X") on the consent document, after taking part in the informed consent process.

If a participant is illiterate:

- Information in the consent materials should be presented orally
- Sufficient time should be allowed for questions to be asked and answered, both by the participant, and by the person obtaining consent to ensure that the participant comprehends the consent information.

Additionally, FDA guidance on Illiterate English Speaking Subjects contains recommendations for documenting the consent process when a participant is competent and understands and comprehends spoken English, but is physically unable to talk or write, but can indicate approval or disapproval by other

*The IRB has and follows written policies and procedures to evaluate the consent process and to require that the Researcher appropriately document the consent process. (**AAHRPP Element II.3.F**)*

means:

- An impartial witness, present during the entire informed consent discussion, signs and dates the consent document,
- Videotaping the consent discussion might be considered,
- The person obtaining consent might document on the consent form the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate.

Participants (or their LARs) must be given a copy of the signed consent document(s), and any other written information provided to participants.

12.3 IRB Review of the Consent Process, including Consent Documents

*The IRB has and follows written policies and procedures to evaluate the consent process and to require that the Researcher appropriately document the consent process. (**AAHRPP Element II.3.F**)*

Principal Investigators (PIs) should refer to HRPP Handbook Section 12.4 for information regarding the development of an informed consent process and method of documentation appropriate to the type of research and the study population.

PIs must submit for IRB review any consent document(s) and explanation of the circumstances under which informed consent will be sought for study submissions.

The study submission solicits the information necessary for the IRB to evaluate whether the informed consent process will be appropriately conducted given the protocol-specific circumstances (e.g., level of risk, inclusion of special participant populations) and adequately protects participants, considering issues such as whether:

14. Participants have sufficient time to discuss concerns and decide whether to participate in the research.
15. The possibility of coercion and undue influence is minimized.
16. Communications to the participant or his/her LAR are in a language understandable to them; and
17. Consent process communications do not include any exculpatory language through which the participant or his/her LAR is made to waive, or appear to waive, any of the participant's legal rights, or which releases or appears to release the investigator, sponsor, institution, or agents from liability for negligence.

The IRB considers the relationship between the person(s) who will solicit, obtain consent, and explain the consent document and the potential participant. The IRB requires that the circumstances of the consent process be culturally and linguistically appropriate for the intended participants and protects participants by minimizing the possibility of coercion and undue influence and allowing adequate time for them to discuss and decide whether to participate in the research.

The IRB determines that all basic, and all additional elements appropriate to the research, are included in the consent process using the Informed Consent Checklist. All the relevant requirements in OHRP in 45 CFR 46.109(b) and 46.116, the FDA regulations in 21 CFR 56.109(b), 50.20 and 50.25 that are applicable to the consent process and the consent document, must be satisfied for IRB approval.

The IRB may require revisions to the consent document as a condition for approval. If the revisions are minor, the protocol may be approved contingent upon the revisions being made. An IRB staff and/or member must confirm that the revisions have been implemented as specified before the contingency can be removed.

The approval date is stamped on the consent document(s).

12.4 Documentation of Informed Consent – Signature Requirements

*The IRB has and follows written policies and procedures to evaluate the consent process and to require that the Researcher appropriately document the consent process. (**AAHRPPElementII.3.F)***

When a person agrees to be a participant in a research study, signing the consent document indicates that he/she has participated in the consent process, and understands the information provided to them.

Documentation of informed consent refers to a participant, or his/her LAR, signing and dating an IRB-approved, dated consent document, which includes the required and applicable additional elements of informed consent (45 CFR 46.116; 21 CFR 50.25(a),(b)).

To approve research, the IRB must determine that informed consent will be appropriately documented, unless the IRB waives documentation under OHRP or FDA regulations (see *HRPP Handbook Section 12.5- Waiver or Alteration of Informed Consent*). If a participant lacks the capacity to consent, then consent for research must be obtained from their LAR. *(*See *HRPP Handbook Sections 12.1- Requirements for Informed Consent* and *12.2- Consent Procedures for Vulnerable and Other Special Populations Including Consent by a LAR.)*

Consent is documented through use of an electronic consent process or written consent document signed and dated by the participant or his/her LAR that embodies all the required elements of informed consent. See *HRPP Handbook Section 12.1- Requirements for Informed Consent* for additional information. Only the IRB approved informed consent document may be used, and unless the requirement is waived by the IRB, the document must be signed by the participant (or the participant's LAR), and a copy must be given to the person signing the form. FDA regulations require that the signature be dated.

12.5 Waiver or Alteration of Informed Consent

*The IRB has and follows written policies and procedures for approving waivers or alterations of the consent process and waivers of consent documentation. (**AAHRPPElementII.3.G**)*

Please note: FDA regulations (governing clinical investigations of FDA-regulated products) **do not** provide for a waiver or alteration of the requirements to obtain informed consent from research participants; the only exceptions to the informed consent requirements are for clearly defined circumstances:

- Emergency use of a test article (see *HRPP Handbook Section 5.7-Other Access to Investigational Drugs and/or Devices*), and
- Planned emergency research (see *HRPP Handbook Section 12.6 - Exceptions to Informed Consent in Emergency Situations*).

Under HHS 45 CFR 46.116, IRBs have authority to alter or waive the requirement to obtain informed consent when research is not FDA-regulated. Please also see Geisinger Guidance - Findings for Waiver or Alteration of Consent Documentation.

The IRB may approve an investigator's request to waive or alter the requirement to obtain informed consent if the investigator demonstrates with specificity that the criteria under 45 CFR 46.116 are met. To approve such a request, the IRB must find and document the following:

18. The research involves no more than minimal risk to the subjects.
19. The research could not practicably be carried out without the requested waiver or alteration.
20. 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.
21. The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
22. Whenever appropriate, subjects will be provided with additional pertinent information after participation.

Special Considerations for Research Involving Deception

In research involving deception, the investigator may, with protocol-specific justification, request an alteration of the consent process. The IRB may approve the research, including the request to alter the requirement for informed consent if the investigator demonstrates that deception or incomplete disclosure is necessary and addresses concerns relating to participant protection (e.g., debriefing).

Waiver of Documentation of Consent

As allowed by OHRP (45 CFR 46.117) and FDA regulations (21 CFR 56.109(c)), the IRB may waive the requirement to obtain written documentation of informed consent. A waiver of documentation of consent does not mean that requirements of the consent process are removed.

Even if a waiver of documentation is granted by the IRB, permitting the investigator to forego obtaining the participant's signature on a written consent document, the investigator still must provide the participant with all the information described in Section 12.1 required to constitute a complete and appropriate consent process, through an information sheet and, or through an oral script in a language understandable to the participants. The IRB may suggest that the Principal Investigator provide participants with an Information Sheet with specific study details outlined.

To approve a waiver of documentation, the IRB must find that the protocol-specific justification for waiving documentation satisfies regulatory criteria. Specifically, the IRB must determine the regulatory basis for the waiver as one of the following:

1. Under HHS 45 CFR 46.117, the IRB must find and document either:
    a. the only record linking the participants and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality. Each participant will be asked whether he/she wants documentation linking the participant with the research, and the participant's wishes will govern; or
2. the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context; OR the IRB must find and document that the research involves no more than minimal risk to participants and involves no procedures for which written consent is normally required outside of the research context. (45 CFR 46.117, 21 CFR 56.109(c)(1))

Waiver or Alteration of HIPAA Authorization

In order to waive or alter an authorization, the investigator must provide sufficient information on which the IRB may make the following three findings specified by the Privacy Rule (45CFR 164.512(i)(2)(ii):

1. The use or disclosure of protected health information (PHI) involves no more than minimal risk to the privacy of individuals based on.
   a. An adequate plan to protect the identifiers from improper use and disclosure.
   b. An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law; and
   c. Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the Privacy Rule would permit the use or disclosure of protected health information.
2. The research could not be practically conducted without the waiver or alteration; and
3. The research could not be practically conducted without access to and use of the protected health information.

12.6 Exceptions to Informed Consent in Emergency Situations

*The IRB has and follows written policies and procedures for making exceptions to consent requirements for planned emergency research and reviews such exceptions according to applicable laws, regulations, codes, and guidance. (**AAHRPPElementII.4.C**)*

Planned emergency research refers to clinical investigations planned for emergency settings, including the planned use of a test article. **Note:** *Planned emergency research* is not the same as *emergency use of a test article*, which is addressed in HRPP Handbook Section 5.7.

Planned emergency research involves an extensive approval process, including FDA approval, prospective IRB review, and approval and consultation with representatives of the communities in which the research will be conducted and from which participants will be drawn. Investigators must submit a study application including a description of the informed consent process or a request to waive informed consent; often in emergency settings it is not possible to obtain informed consent from a potential participant when there is insufficient time and/or a LAR is not available.

The IRB may approve a request for an **exception from informed consent requirements for emergency research** if all requirements outlined 21 CFR 50.24 (FDA) are met. Under these regulations, the IRB may permit planned research in an emergency setting without the informed consent of the participants or his/her LAR in a limited class of emergent situations where the participant needs an emergency experimental intervention but cannot give informed consent due to a life- threatening medical condition and there is not sufficient time to obtain consent from the participant's LAR.

Also refer to the following resources for additional information:

- **Informed Consent Requirements in Emergency Research (OPRR Letter, 1996)**

- **FDA Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors Exception from Informed Consent Requirements for Emergency Research**

12.7 Observation of the Consent Process

*Geisinger has and follows written policies and procedures that allow the Institutional Review Board to function independently of other organizational entities in protecting research participants. (**AAHRPP Element I.1.C**)*

As part of the IRB oversight options, the IRB may require that a staff member or a third party observe the consenting of research participants to determine:

- Whether the informed consent process has been appropriately completed and documented.
- Whether the participant has had sufficient time to consider study participation, and that no coercion has been used by the consenting staff; and
- That the information presented to the participant reflects the content of the consent form and is conveyed in understandable language.

The IRB may require that one or more informed consent process situations be observed for selected protocols. IRB considerations used to choose such protocols include:

- High risk studies
- Studies that involve particularly complicated procedures or interventions
- Studies involving potentially vulnerable populations (e.g., ICU patients, children)
- Studies involving study staff with minimal experience in administering consent to potential study participants, or
- Situations when the IRB has concerns that the consent process is not proceeding well.

The *Charge to Geisinger IRB Members by Geisinger's Institutional Official (IO)* includes the statement, "Geisinger Institutional Review Board (IRB) Members are assigned the authority and responsibility to perform, in an independent and autonomous manner, the key functions of the Human Research Protection Program (HRPP) of Geisinger Clinic and its components named in Geisinger's Federalwide Assurance (FWA) and affiliates."

Section 13 – Multi-site Research Under Reliance

13.1 Reliance Agreements

Geisinger regularly enters into reliance agreements when participating in multi-site research, both to rely on external reviewing IRBs and to provide single (sIRB) services for a multi-site research. Geisinger enters into reliance agreements for both multi-site research subject to federal sIRB mandates, such as the NIH Single IRB Policy and the Common Rule Cooperative Research Rule, as well as multi-site research that is not subject to a federal sIRB mandate.

Geisinger is a SMART IRB participating institution and has signed SMART IRB Agreement v2.0, which incorporates revisions to the original SMART IRB Agreement that enable the NIH to participate in the Agreement.

Geisinger employs flexibility when executing reliance agreements but prefers to use the SMART IRB Online Reliance System. Geisinger is willing to use its own template or another institution's reliance agreement in existing or modified form and enters into master reliance agreements to cover multiple protocols. Regardless of the mechanism used, reliance agreements are composed of terms that delineate the roles and responsibilities of both the reviewing and relying institutions. Prior to execution, Geisinger is willing to enter negotiations with another institution to modify outlined terms and conditions, as necessary.

Please see additional details about reliance agreements in:

- *Geisinger IRB Investigator's Guide for Geisinger Serving as the Single IRB*
- *Geisinger IRB Investigator's Guide for Relying on an External IRB*

13.2 Geisinger as the Reviewing IRB

Geisinger's sIRB policies, processes and requirements are detailed in a sperate document titled: *Geisinger IRB Investigator's Guide for Geisinger Serving as the Single IRB.* This document is the primary sIRB resource and serves as a comprehensive guide for all investigators and participating site stakeholders.
All IRB records related to Geisinger's sIRB review and oversight are indefinitely maintained within iRIS, Geisinger's electronic submission platform.

13.3 Geisinger as the Relying Institution

Geisinger's reliance policies, processes and requirements are detailed in a separate document titled: *Geisinger IRB Investigator's Guide for Relying on an External IRB*. This document is the primary reliance resource and serves as a comprehensive guide for all investigators and non-Geisinger stakeholders involved in the reliance process.
All HRPP records related to Geisinger's HRPP/local context review, including ceding determinations, are indefinitely maintained within iRIS.

Section 14 – Information Management in Multi-Site Research

*The IRB has and follows policies and procedures for managing multisite research by defining the responsibilities of participating sites that are relevant to the protection of research participants, such as reporting of unanticipated problems or interim results. (**AAHRPP Element II.2.H**)*

14.1 Geisinger Serving as the Coordinating Institution

The PI is responsible for serving as a liaison with other participating organizations and with regulatory and funding agencies. It is the policy of Geisinger IRB for the PI to assure that all facilities participating in a human subjects study receive adequate information about the study in order to protect the interests of study participants when Geisinger is the coordinating center. The PI is responsible for adopting all protocol modifications in a timely fashion and for ensuring that the research study is reviewed and approved by any other appropriate committees at the coordinating center and at the participating organizations prior to enrollment of subjects.

Before a study can begin, it must be approved by the IRB of record for each participating organization, and where appropriate, the IRB of record for the coordinating center. The PI is responsible for ensuring that all participating organizations obtain review and approval from their IRB of record and must collect and maintain documentation of IRB approval for each participating institution.

A Geisinger PI wishing to act as the coordinating center for a multisite research effort must submit an application for GIRB review and approval which describes the coordinating center functions and responsibilities. The PI may submit either of the following to GIRB:

1. **For studies in which there will be no subject enrollment at Geisinger**, an application and protocol that outlines the responsibilities of the center and the coordinating PI must be submitted for IRB review and approval prior to initiating the center's functions.
2. **For studies in which there will be subjects enrolled at Geisinger**, an application and protocol which outlines the conduct of the research with participants at Geisinger must be submitted for review and approval. In such cases, a specific coordinating center protocol may be developed and submitted as a separate protocol for review and approval. If a separate protocol is not developed, the coordinating center and coordination PI functions must be described in the main study protocol.

In either case, GIRB will confirm that the following are addressed by the PI in the description of the coordinating center and its functions:

- Name of each participating institution
- Name of PI at each participating institution
- Name of IRB of Record for each participating institution
- Confirmation that the coordinating center PI has contact information for all sites
- Confirmation that each participating center has on file an active FWA with OHRP

- A method for assuring that all sites have the most current version of the protocol and that amendments to the protocol will be communicated to all sites.
- A plan for collection and management of data from all siters as applicable.
- A process for reporting and evaluating protocol events and deviations from participating sites.

If a participating site does not have an IRB or desires Geisinger IRB to serve as the Reviewing IRB for that site, that site may request that the Geisinger IRB serve as the IRB of Record. The requirements outlined in *Geisinger IRB Investigator's Guide for Geisinger Serving as the Single IRB* will be followed for all sIRB arrangements.

For Single IRB Studies, in addition to the above criteria, the following must also be addressed in the multi-site protocol:

- A plan for collection of annual enrollment data from all sites for submission with the continuing review
- A plan for how sites will be educated about applicable GIRB policies, including the Geisinger Prompt reporting requirements
- A description of how the coordinating center will monitor protocol events and deviations and ensure appropriate reporting to GIRB

14.2 Reporting unanticipated problems and non-compliance to the IRBs in Multi-Site Research

As the lead investigator at the coordinating institution, the Geisinger PI is responsible for receiving data and reports related to serious or continuing non-compliance and/or unanticipated problems from the outside sites in a timely manner and distributing them to the Geisinger IRB in accordance with applicable polices:

1. Geisinger serving as the sIRB – Follow Prompt reporting polices in the *Geisinger IRB Investigator's Guide for Geisinger Serving as the Single IRB*
2. Geisinger relying on an External IRB – Follow the prompt reporting polices in the *Geisinger IRB Investigator's Guide for Relying on an External IRB*
3. Multi-site research not under reliance – Follow the prompt reporting polices in *HRPP Handbook Section 3.8 – Prompt Reporting for Reportable Events* when the event directly impacts participants enrolled at Geisinger or a Geisinger affiliated site.

Section 15 - Investigator Requirements

15.1 Qualifications and Training of the Principal Investigators (PIs) and Training in the Protection of Human Subjects

> *Researchers and Research Staff are qualified by training and experience for their research roles, including knowledge of applicable laws, regulations, codes, and guidance; relevant professional standards; and the Organization's policies and procedures regarding the protection of research participants. (**AAAHRPP Element III.2.A**)*

Geisinger's Research Education and Training Policy applies to all investigators and members of the research staff (including persons not employed by Geisinger but conducting research at a Geisinger entity), non-traditional research personnel (including persons such as students, volunteers, or interns), compliance committee members, HRPP staff, IRB members. This policy outlines research training requirements that must be completed through the Collaborative Institutional Training Initiative (CITI) online platform. The following training courses must be completed and are valid for three (3) years: 1) Human Subjects & Data Only Researchers & Staff, IRB Members & Staff, 2) RCR for Researchers, Research Staff, and Administrators, and 3) Good Clinical Practice.

Refer to the following documents for additional information:

- Geisinger's Research Education and Training Policy
- HRPP Handbook Section 4.3 - Required Training in Human Research Protections

Knowledge of Applicable Federal, State and Local Laws

The Institutional Review Board provides resources and education related to federal, state, and local laws available to the Geisinger research community via the IRB website and training to promote knowledge about applicable federal, state, and organizational policies for human subjects' research. Examples include:

- Geisinger policies, including this HRPP Handbook
- Guidance documents on topics affecting the conduct of research, such as informed consent, vulnerable populations, conflict of interest, reporting requirements, etc.
- Template consent forms that include federal, state, and local requirements
- iRIS System for protocol submission - with study application questions intended to address required considerations
- Information and instructions on submitting protocols to the IRB
- References and links to federal, state, and organizational requirements
- Contact information for IRB staff assistance

Where applicable, the Pennsylvania State laws have been referenced in the Geisinger HRPP Handbook. (e.g., regulations related to use and disclosure of mental health, substance use disorder treatment and HIV-related medical records, age of majority, legally authorized representatives).

When Geisinger investigators conduct research in states other than Pennsylvania, they are expected to be knowledgeable of and adhere to the laws of the state in which research is being conducted, as well as those of Pennsylvania. Investigators are advised to seek guidance from the IRB staff if they have questions as to the applicable laws.

Knowledge of the Definition of Human Subject Research

> *Researchers and Research Staff know which of the activities they conduct are overseen by the Human Research Protection Program, and they seek guidance when appropriate. (**AAHRPP Element III.1.A**)*

Prior to IRB submission investigators are instructed to consider whether their project meets the statutory definition of "human subject research" as defined by HHS in 45 CFR 46.

IRB staff is available to assist investigators in determining if a project needs to be submitted for IRB review. If the proposed activity clearly does not involve "research" and "human subjects", it does not require submission to the IRB. If there is any doubt as to whether an activity is human subject research and/or if the investigator would like documentation that IRB staff reviewed and determined his/her project is "not human subjects research", the investigator should submit a Research Determination Worksheet (RDW) via iRIS. IRB staff will review to make a determination of whether the proposed project includes human subjects research and send a Determination letter to the investigator as documentation of the review and outcome.

See *HRPP Handbook Section 3.3 - Regulatory Definition of Human Subject Research* for additional information on the definition of human subject research.

Additional details are provided in the following sections of the HRPP Handbook:

- *Section 1.6 - Ethical and Legal Principles Governing Human Subject Research*
- *Section 3.1 - Policies and Procedures Available to Principal Investigator's (PIs) and Research Staff*
- *Section 4 - Knowledge of Human Research Protection Requirements, for an outline of education provided for individuals responsible for human research, and description of the required training*
    - *Section 5.6 - Sponsor-Investigator Research:*
    - *Section 3.1 - Agreement Includes Protection for Research Participants*

15.2 Reporting to the IRB – Reportable Events (Unanticipated Problems Involving Risks to Participants or Others and Other Reportable Information)

> *Researchers and Research Staff follow reporting requirements during a research study in accordance with applicable laws, regulations, codes, and guidance; Geisinger policies and procedures; and the IRB's requirements. (**AAHRPP Element III.2.D**)*

PI Responsibilities

Prompt Reporting for Reportable Events

When conducting human subjects research certain events may occur which require timely notification to the IRB. While these events are not desirable and sometimes unpreventable, to ensure the safety and protection of human participants in their research, investigators must assess such events and follow the reporting policies within this *HRPP Handbook Section 3.8 – Prompt Reporting for Reportable Events.*

Events that may meet the criteria of unanticipated problems involving risk to participants and others and serious or continuing noncompliance are reportable events that require prompt reporting to the IRB. Other events, such as minor protocol deviations or minor noncompliance, do not require prompt reporting to the IRB; however, must still be tracked and documented in the research team's files, and reported to the IRB at the time of continuing review, if applicable.

Routine, periodic reports (e.g., Data Safety Monitoring Committee (DSMB) reports, annual progress reports) should be submitted to the IRB at the time of the Continuing Review submission. The Prompt Report Form ***should not*** be used to submit DSMB reports to the IRB. IF a DSMB report indicates new or increased risk to participants, investigators should submit the report via Amendment/Modification form summarizing the change in risk and investigator response to mitigate risk and/or inform participants (e.g., protocol modifications, informing participants, revised informed consent).

Important details about this topic are found in *HRPP Handbook Section 3.8 – Prompt Reporting for Reportable Events.*

15.3 Research Oversight

*Researchers maintain appropriate oversight of each research study, as well as Research Staff and trainees, and appropriately delegate research responsibilities and functions. (**AAHRPP Element III.2.B**)*

Federal regulations require that any research study involving human subjects be reviewed and approved by an IRB. IRB approval must be obtained before any research activity involving human subjects begins.

It is the PI's responsibility to submit a study application for all proposed human subjects research to the IRB for review. At submission, the obligations of the PI with respect to oversight of their research and research staff during recruitment, selection of study participants, and conduct of the study according to the protocol as approved by the IRB are stated in the study submission and must be agreed to by the PI for the submission to be accepted. The PI is responsible for ongoing adherence to the determinations and requirements of the IRB for the duration of the research.

The documents required for protocol submission are listed in *HRPP Handbook Section 8.1 - IRB Protocol Files*.

Continuing Review Reporting
PIs must submit continuing review reports for FDA-regulated clinical investigations to the IRB before the study approval expiration date and in sufficient time to ensure the non-interruption of approval of studies. The IRB recommends submitting the continuing review submission approximately 60 days before the study's expiration date to allow time for adequate review.

Removal of Continuing Review Requirement (as permitted in 2018 Revised Common Rule)
Effective May 1, 2018, GIRB applied flexible provisions adapted from the *Final Revised Common Rule 45 CFR 46 Subpart A - Basic HHS policy of Protection of Human Research Subjects (January 18, 2017)* to research that was neither federally-sponsored nor FDA-regulated. As such, GIRB eliminated the continuing review requirement for most minimal risk research and required documentation of rationale for continuing review of research that otherwise would not require continuing review.

New studies determined to be minimal risk and approved on or after January 21, 2019 (and ongoing studies that did not already transition prior to this date) are evaluated to assess criteria to remove the requirement for continuing review at the time of the study approval or continuing review occurring on or after January 21, 2019. The determination is based on investigator responses to questions related to sponsor or regulated status (e.g., studies subject to FDA regulations must undergo continuing review regardless of risk level), status of participant interaction and research activities and the criteria outlined below. Continuing review requirements are communicated to the study PI in the Review Outcome Letter and documented in the study's electronic IRB record, and Continuing Review and Expiration dates are removed from the Study Outcome tab and Outcome letter when the IRB reviewer determines continuing review is not required.

If the IRB determines continuing review is required for research that otherwise would not require continuing review as described below, the rationale for conducting continuing review of research will be documented in the IRB records and communicated to the investigator.
Removal of the requirement for continuing review does not impact other IRB submission requirements, e.g., any modifications to the IRB-approved protocol, documents, study personnel, etc. must be submitted for IRB approval prior to implementation of the change. In addition, this does not remove the requirement for reporting to the IRB any Unanticipated Problems (UPs) that increase risk to participants or non-compliance that meet criteria for Prompt Reporting.

> ***HRPP Handbook Section 7.4 - Assignment of protocols to IRB members*** outlines the criteria for determining ongoing continuing review of research is **not required.**

Final Report

Upon completion of human subjects' research, investigators must submit a Final Report to the IRB notifying the IRB of the completion of the research.

Confidentiality of Records and Personal Data

PIs working with human subjects must safeguard the privacy of participants and protect the confidentiality of personal information:

- Safeguard mechanisms must be established, maintained, and documented throughout the research process.
- Sustained attention must be paid to maintaining confidentiality of research data in the design, implementation, conduct, and reporting of research.
- Full information about the privacy and confidentiality of data must be provided to prospective participants through the informed consent process.
- Unintentional breaches must be avoided by taking additional precautions in communication, administration, and storage of information.

Refer to *HRPP Handbook Section 11 - Privacy and confidentiality* for detailed information related to protecting participant privacy and data confidentiality

Privacy Rule (HIPAA)

When conducting research that involves the use and disclosure of protected health information (PHI), the PI must abide by the applicable Geisinger HIPAA policies and must submit an accounting of disclosures of PHI to Geisinger's System Privacy Office at the time of PHI disclosures within research for which the IRB has granted a waiver of HIPAA authorization. See *HRPP Handbook Section 11.3-HIPAA - Health Insurance Portability and Accountability Act Regulations* for additional information.

Highly protected health information (HPHI) is defined by Geisinger Institutional Policy as PHI that is protected by federal or state laws that are more restrictive than HIPAA. Collectively this information is referred to as HPHI. At Geisinger, the following types of information are considered HPHI.

- Mental Health Records
- Substance Use Disorder Records
- HIV-Related Information

Please refer to *HRPP Handbook Section 11.4, Highly Protected Health Information* for additional information.

Delegation of Research Responsibilities

Principal investigators must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility. The conduct of a study usually requires the involvement and contribution of other individuals under the direction of the PI, based on their qualifications and capabilities. In delegating study-specific tasks and responsibilities to other members of the research team, the PI must ensure that those assuming a duty are adequately trained and qualified by education and experience to perform delegated responsibilities. Delegation of responsibilities by the PI should be clearly documented and maintained within the study files (e.g., Delegation of Authority log).

Special Considerations for the Oversight of Research Protocols in FDA-Regulated Drug or Device Studies

FDA regulations and guidance specify the responsibilities of sponsors (and their investigators) using FDA test articles. [21 CFR 312 Subpart D; 21 CFR 812 Subparts C, E]. FDA requirements are also summarized in Geisinger

Guidance - Special Considerations for the Oversight of Research Protocols in FDA-Regulated Drug or Device Studies.

21 CFR 312.3(b) defines ***sponsor-investigator*** as an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. In ***sponsor-investigator research***, the PI assumes all the responsibilities in overseeing the clinical investigation normally assumed by the sponsor in industry-sponsored projects. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

Refer to the following resources for additional information:

- *HRPP Handbook Section 5.4 - Sponsor-Investigator Research*
- *Geisinger Guidance – Sponsor-Investigator*

*Researchers and Research Staff follow the requirements of the research protocol or plan and adhere to Geisinger policies and procedures and to the requirements or determinations of the IRB. (**AAHRPP Element III.2.C**)*

Study Conduct

The PI is responsible for conducting the study in a manner that is scientifically and ethically sound and for ensuring the use of appropriate methods and correct procedures, according to the approved protocol. Any new information, modification, or unanticipated problem involving risks to participants or others must be promptly reported to the IRB. Research participants must be informed of any change that may affect their willingness to participate.

The PI must ensure that all personnel under his or her supervision are adequately trained and supervised and that research duties are delegated to individuals qualified to perform the assigned tasks.

The PI is also responsible for the timely and proper administration of the research project. Beyond the scientific and clinical conduct of the study, responsibilities include:

- Compliance with federal, state, local laws and Geisinger policies, including disclosure of any potential conflict of interest
- Adhering to Geisinger's Code of Conduct
- Fiscal management of the project
- Training and supervision of fellows, residents, and any other research personnel involved in the study.
- Compliance with the sponsor's terms and conditions (e.g., non-disclosure of sponsor confidential information)
- Submission of all technical, progress, financial, and invention reports on a timely basis
- Submission of amendment/modification and continuing review applications in a timely manner
- Obtaining approval for changes prior to implementation.

Oversight of Research Staff during Recruitment

The PI is responsible for ensuring all recruitment methods and activities are described in the study submission and IRB-approved.

Selection of Study Participants

The PI must ensure selection of study participants is equitable and appropriate to the goals of the study. Adequate safeguards for the protection of participants during the recruitment and conduct of research must be set forth in the study submission.

For additional information, refer to:

- *HRPP Handbook Section 10.1 - Equitable Selection*

Informed Consent

PIs are responsible for assuring the quality of the informed consent process and for making sure that consent is obtained and documented before subject participation unless the IRB approves a waiver of consent.

The PI must ensure that informed consent is obtained from each research participant before that individual participates in the research study. The PI may delegate the task of obtaining informed consent to another study team member who is qualified by education and experience and adequately trained about the research; however, if the research involves an investigational product, a licensed physician-investigator must participate in the informed consent process by explaining to the potential participant information about the investigational product, including potential risks, benefits and alternatives. PI delegation of the responsibility of obtaining informed consent should be clearly documented and maintained within the study files (e.g., Delegation of Authority log).

For a detailed discussion of the informed consent process requirements and description of available templates and guidance, see *HRPP Handbook Section 12 – Informed Consent and Assent*.

15.4 Data Monitoring Plan (DMP)

*Researchers and Research Staff follow reporting requirements during a research study in accordance with applicable laws, regulations, codes, and guidance; Geisinger policies and procedures; and the IRB's requirements. (**AAHRPP Element III.2.D**)*

The responsibility for human participant protection in human subject research is shared among the IRB, PI, trial sponsors and oversight boards or committees. The safety of participants must be considered in study design. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. (45 CFR 46.111; 21 CFR 56.111(a) (6))

There are several aspects that are considered when determining the type of monitoring required for the study, particularly the risk level of the study. It could be as simple as the protecting the data (how data is protected, who has access, are you collecting the minimum necessary, etc.) in a retrospective data collection study or more

robust in a more than minimal risk clinical investigation, which will require a data safety monitoring plan and analysis and reporting of safety information and adverse events to the sponsor, IRB and applicable external agencies (e.g., FDA for FDA-regulated research).

Monitoring may be conducted by the PI, or other means. In all studies, the PI has ultimate responsibility for identifying potential risks and identifying adverse events occurring in the study population and reporting the events to the sponsor and to the IRB as required by Geisinger IRB. Please see *HRPP Handbook Section 3.8 – Prompt Reporting for Reportable Events* for details related to Geisinger IRB reporting requirements.

Sponsor Responsibilities

Sponsor responsibilities may include (but are not limited to), as appropriate to the scope and complexity of the research:

- Establishing procedures to ensure that interim data remains confidential
- Notifying all participating IRBs of Unanticipated Problems involving risks to participants or others
- Notifying FDA and the responsible IRBs of any recommendations or to the sponsor that address safety of participants.

In sponsor-investigator research, the PI assumes all the responsibilities in overseeing the research normally assumed by sponsors in industry-sponsored projects.

DEFINITIONS:
Minimal risk 45 CFR 46.102 - (HHS) is defined as 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.

Studies that are more than minimal risk to participants must include a data monitoring plan (DMP) to evaluate whether the character, incidence, and severity of expected harms match those expected, and to evaluate the causality of unexpected harms. Requirements for a DMP are discussed in Guidance – Data and Safety Monitoring. Additionally, a description of the DMP is required in the study submission to the IRB. To approve research, the IRB determines that when appropriate, there will be adequate monitoring of data to protect the safety and well- being of participants.

Sponsor 21 CFR 312.3 – (FDA) means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

If there is a Data Safety Monitoring Committee, sponsor responsibilities may include:

- Appointing a Chair
- Establishing procedures to assess potential conflicts of interest of proposed members

- Establishing Standard Operating Procedures (SOPs) for statistical analyses, report format, and meeting schedules
- Submitting SOPs to the FDA prior to interim data analyses, optimally before the initiation of the trial.

Section 16 - HRPP Coverage of Sponsored Research

Geisinger Human Research Protection Program Policy states, "The HRPP exists to promote high quality, ethical research. The HRPP serves as the advocate for the rights and welfare of persons who participate in human subjects' research conducted at Geisinger and all affiliate organizations for which there is an agreement to provide services related to the HRPP.

Geisinger's policy for the protection of human participants is guided by ethical principles, Federal law, and institutional standards. The guiding ethical principles are embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Compliance with this policy provides protections for human participants as mandated by applicable laws, regulations, and standards of local, state, and Federal government agencies concerning the protection of human participants, including the U.S. Code of Federal Regulations (CFR):

- 45 CFR 46, Protection of Human Subjects, U.S. Department of Health and Human Services (DHSS), Office for Human Research Protections (OHRP), and
- 21 CFR 50, 56, 312, 600 and 812 of the Food and Drug Administration (FDA)

All researchers involved in human subject research must abide by the specific operational standards, policies and procedures outlined in the HRPP Handbook and Guidance Documents."

16.1 Agreement Includes Protection for Research Participants

*Geisinger has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board, as appropriate. (**AAHRPP ElementI.1.D**)*

Geisinger addresses the protection of research participants by:

- Including in standard contract templates a provision that the sponsor acknowledges and understands that the Geisinger HRPP is applicable to all human participant research.
- Asking for the inclusion of such a provision in any proposed contract that does not use their standard templates
- Including in the cover letter accepting and acknowledging the grant an equivalent statement regarding the HRPP in grants to Geisinger.

Additionally, the IRB will review the proposed consent form and delete any provision that requires a participant to waive or appear to waive any legal rights (i.e., exculpatory provisions).

16.2 Provision Addressing Medical Care for Participants

*Geisinger has a written agreement with the Sponsor that addresses medical care for research participants with a research-related injury, when appropriate. (**AAHRPP Element I.8.A**)*

In sponsored research, medical care for participants is addressed by:

- Including in its standard contract template a provision that the sponsor provides for the cost of diagnosis, care and treatment of any undesirable side effects, adverse reactions, illness, or injury to a participant, without regard as to the fault of the sponsor
- Asking for the inclusion of such a provision in any proposed contract that does not use Geisinger's standard template
- Including the substance of any such provision in the consent form
- Including a statement in the consent form that participants do not waive any liability rights for personal injury by signing the consent form.

Sponsored research: Research funded by external entities through a grant or contract that involves a specified statement of work (e.g., the research proposal) with a related transfer of value to the sponsor, including clinical trials involving investigational drugs, devices, or biologics.

Section 17 - Communication from Sponsors Affecting IRB Oversight

17.1 Data and Safety Monitoring (DSM) in sponsor agreements

Geisinger has included in their standard sponsored research contract templates, provisions that the sponsor will notify the Principal Investigator or the IRB of:

1. Non-compliance with the protocol or applicable laws, particularly those laws related to participants, which could impact the safety or welfare of the participants
2. Serious adverse events that have been reported to the FDA or other governmental agency in relation to the protocol at Geisinger or any other site
3. Unanticipated Problems in the protocol at Geisinger or any other site that could relate to risks to participating participants, and
4. Circumstances that could affect participants' willingness to continue to participate in the protocol or the IRB's continuing approval of the protocol.

When non-standard contract templates are used, the sponsor is asked to include equivalent statements. See "Clinical Trial Agreement Memo".

Data and Safety Monitoring (DSM) in sponsor agreements

For sponsored research, Geisinger agreements specify that, as appropriate:

- Provisions are made for monitoring study data which could affect participants' safety.
- The results of this monitoring are reported to the researcher (PI) so that:
    - Routine monitoring reports will be submitted as part of Continuing Review submissions to the IRB, and
    - Urgent reports (those meeting the criteria for prompt reporting) are submitted to the IRB according to the guidelines specified in HRPP Handbook Section 3.8 – Prompt Reporting for Reportable Events.

Section 18 - Knowledge Benefit and Participant's Interests

18.1 Publication of Research Results

Geisinger establishes the importance of disseminating research findings as one of its most important processes for human subject research.

Geisinger requires that provisions for fair and reasonable ownership of data and research results be included in its sponsored research agreements and has a process that allows investigators to place their inventions in the public domain if that would be in the best interest of technology transfer and if doing so is not in violation of the terms of any agreements that supported or governed the work. Researchers must follow requirements outlined in institutional policies related to inventions, licensing, and intellectual property.

18.2 Communicating Study Results to Participants

When the IRB learns of events that could affect participant welfare after a study has closed (e.g., an investigational product studied at Geisinger is withdrawn by the FDA), the IRB seeks information, deliberates, and considers whether (and how) to contact participants who might be affected. Even when the study is not yet closed, but participants have completed participation, the PI must inform former participants when information is learned that could affect their welfare.

For sponsored research, Geisinger addresses communication with sponsors regarding the impact of research results on participant health and safety including a provision within the contract that the sponsor will develop a plan of communication with the Principal Investigator that is acceptable to the IRB when new findings or results of the protocol might:

- impact the willingness of subjects to continue to participate in the protocol,
- directly affect their current or future safety or medical care, or
- by asking for the inclusion of such a provision in any proposed contract that does not use their standard template.

Section 19 - Addressing Concerns of Research Participants

19.1 Consent Form Requirements

The IRB requires that all informed consents include contact information for the investigator(s) conducting the research study. Participants are instructed to call the investigators if they have any questions about the research, about their rights as a research participant, or if they believe they have suffered a research-related injury. Clinical trial informed consents include the hospital's 24-hour contact number that can be used to reach study investigators.

Each consent form must also include telephone numbers for the IRB. The IRB contact information affords current or past research participants or their designated representatives a means to contact an informed individual who is independent of the research team. The IRB also serves as a conduit for receiving information from any party who is not satisfied with the way a study is (or was) being conducted, or if any party has any concerns, complaints or general questions about research or the rights of research participants.

Consent form templates available on the HRPP website, include instructional text and verbatim language for the inclusion of the investigator's contact information and IRB telephone numbers under the consent form heading "Contact Information."

19.2 Recruitment Material Requirements

The IRB requires specific contact information to be included in participant recruitment materials– flyers, newspaper ads, newsletters, and web postings. Geisinger Guidance - Advertisements / Appropriate Language for Recruitment Material provides appropriate language to include in recruitment material.

All recruitment materials must include the appropriate contact information for the investigator(s) conducting the study. The IRB reviews all recruitment materials, and the addition of IRB contact information is required when appropriate.

Telephone (Screening) Scripts
The IRB requires investigator and IRB contact information be included in telephone scripts. Telephone scripts are often used to screen prospective participants. Like the consent forms, telephone scripts must include telephone numbers for IRB (a local number and a toll-free number), as well as telephone numbers for the investigators. This contact information provides prospective participants with channels of communication to the investigators and the IRB for questions, concerns, input, information, or complaints.

Section 20 - Education and Outreach

20.1 On-line Resources and Educational Materials

Geisinger Research Website (Geisinger.org)

Geisinger Research website contains multiple microsites to inform Geisinger patient, clinical, learning and research communities about Geisinger's learning activities, including research and innovation and provides opportunities for patient engagement in learning activities:

- Innovation & Research - provides the history and overview of Geisinger research, including webpages devoted to research administration, core services, and resources (e.g., HRPP and Research Ethics and Consultation)
- Departments & Centers – provides an overview of research centers and institutes, as well as clinical departments and institutes conducting research
- Get Involved – Describes opportunities for patients to be involved with research and innovation activities at Geisinger through webpages focusing on:
  - Research participant
  - Research advisor
  - Research co-investigator
  - Research contributor
- Find an Investigator – provides a search tool to locate investigators or research focus.
- Find a Study – provides information about studies, which includes a brief description of the study, condition being studied, and contact information to learn more about the study
- News – provides recent publications and news articles about Geisinger's research program.

Association for the Accreditation of Human Research Protection Programs (AAHRPP)
AAHRPP is an independent, non-profit accrediting body, ensuring that accredited programs, such as the Geisinger Human Research Protection Program (HRPP), meet rigorous standards for quality, participant protection, and ethically sound research.

Information about accredited programs, and about being a research participant, is available on the AAHRPP website.

20.2 Participant Research Inquiries

Information about Geisinger's human research studies and opportunities for community member involvement as partners in research can be found in the following resources:

1. Get Involved with Research at Geisinger
2. Learn About Clinical Studies
3. Become a Research Volunteer
4. Becoming a Research Volunteer: It's Your Decision

5. MyChart – a secure, web-based patient portal – allows patients to read their medical records, communicate with their caregivers, request appointments, and have access to decision support and trusted healthcare resources. Patients are encouraged to take an active role in their healthcare.
6. **Advancing Healthcare** - Research has been a fundamental and critical aspect of Geisinger since its founding almost 100 years ago. Research is part of Geisinger's Mission and Vision. Dr. Harold Foss, the first leader of the George F. Geisinger Memorial Hospital believed that research would lead to better care for patients. Today, Geisinger's commitment to research is increasingly tied to improving patient outcomes and focusing on building a comprehensive personalized healthcare program. Geisinger encourages everyone to participate in research.
7. **Role Change** - Participation in research studies allows doctors, nurses, researchers and Geisinger patients to work together to improve medicine. Geisinger is involved in research from basic science to clinical trials of the newest drugs and medical procedures. Research is an option for everyone - healthy members of the Geisinger family and patients with current medical concerns have the opportunity to join studies to examine causes of disease, ways to prevent diseases, and new treatments. Research can make a difference and your participation is important - pediatric cancer physicians enroll 50%to 80% of all children with cancer in research studies.
8. **Opportunities for Everyone** – Provides specific details about research programs that need all type of participants - healthy individuals, individuals known to be at risk for certain medical conditions and individuals currently being treated for a medical condition.
9. **What's New in Research?** – Provides details about research at Geisinger.

20.3 Community Participation in Research

Geisinger is a nationally recognized, integrated healthcare delivery system with a record of clinical innovation, rich resources of clinical data and sophisticated analytics, and an explicit commitment to becoming a patient-centered, patient-participant-engaged Learning Healthcare System (LHS). As such, members of the community have been engaged in Geisinger innovation and research initiatives.

Members of the community have long been engaged in Geisinger innovation and research initiatives. The largest research initiative to continually engage our patient community is Geisinger's MyCode Community Health Initiative. In 2007, Geisinger established this biobank to advance health related (predominantly genetic and genomic) research; since then, the MyCode Community Health Initiative has grown into one of the world's largest biobanks and programs for genomic discovery, with more than 320,000 consented participants, all Geisinger patients, some 3.5 percent of whom are also predicted to receive clinically actionable genomic findings relevant to their own health care through the Genomic Screening and Counseling Program, which incorporates Learning Healthcare System (LCS) principles.

Patient-participant engagement-via surveys, focus groups, and interviews with participants-has been integral to MyCode's development, from its conception to the present day. From the very beginning, MyCode investigators used surveys and focus groups to solicit the perspectives of community members and patients on key policy decisions, including:

- Whether to establish a biobank.
- Whether to return genomic results.

- How to navigate the ethical and psychological complexities of returning genomic results to pediatric participants.
- And most recently, what topics are—and are not—appropriate for genomic discovery research using the DNA and clinical information in participants' EMR.

The MyCode Ethics Advisory Council--an independent, external body numbering nine members, including six community representatives--provides advice on ethical and policy matters to the MyCode Governing Board and the Chief Scientific Officer.

Over the past several years, additional Geisinger investigators have included patient/community representatives in such roles as advisors and investigators. Two Patient Centered Outcomes Research Institute (PCORI)-funded research examples of this are:

1. Putting Patients at the Center of Kidney Care Transitions
2. Enhancing Genomic Laboratory Reports to Enhance Communication and Empower Patients

Several recent efforts have aligned Geisinger more closely (and explicitly) with the LHS model. The first was the formation, in 2013, of an ad hoc, multidisciplinary working group (with representatives from clinical innovation, quality and safety, bioethics, research and compliance, pediatrics, health services research, and other institutional functions), organized around the goal of realizing Geisinger's potential as an LHS. In 2014, Geisinger's revised strategic plan for research yielded two primary recommendations: (1) that Geisinger explicitly embrace the Learning Health System model as an aspirational goal and (2) that patient-engaged research become the default rather than the exception for all Geisinger research involving human participants. Since then, this multidisciplinary working group, which includes a community member, has sought to advance awareness of the potential of patient engagement among Geisinger faculty and investigators; build infrastructure (including personnel, policies and procedures, and facilities); recruit patients to serve as advisors, co- investigators and participants in various types of learning activities; and pilot and assess various strategies for engagement.

In June 2016, with funding from a PCORI Eugene Washington Engagement Award, this working group convened a symposium - Enhancing Patient and Family-Centered Care through Learning, Discovery and Engagement -- that brought together nearly 300 attendees, including clinicians, investigators, institutional leaders and more than 80 Geisinger patients to develop a conceptual map for practically linking and integrating Geisinger's endeavors on three interrelated fronts: (1) realizing the institution's LHS-related aims, (2) improving the experience and quality of care, and (3) advancing patient engagement in research innovation, and quality improvement, enabling those who are interested and willing to become involved in these learning activities as study team members, advisors, and co-investigators. Patients participated in the symposium planning committee and led a workshop designed for prospective patient-participants with an interest in serving as study team members, advisors, and co-investigators for learning health activities.

This working group, now formally referred to as Geisinger's Patient Engagement in Research Working Group, is engaged in a four-phased effort to spur further progress toward the goals of becoming a fully realized learning healthcare system and maximizing patient engagement in learning activities through its five subgroups, each with different, yet interrelated charges:

1. Informed Consent Accessibility – Improve process and content of research informed consents: transparency; flexibility of approach; effectiveness

2. Patient Engagement Infrastructure – Staffing; facilities; policies and processes
3. Patient Engagement Metrics – Review key findings in literature; propose metrics for use and validation
4. Patient/Partner Recruitment Strategies – Develop a pool of prospective partners; identify and deploy recruitment strategies
5. Communication Strategy – Broadly communicate our patient engagement priority; educate and inform Geisinger family, patients, and community; publicize and broaden awareness

Other research and innovation initiatives have formed advisory groups that are largely (if not totally) populated by patients, i.e., community members, who provide oversight to ensure that Geisinger's healthcare learning, discovery and research practices and proposals address patient and community needs and interests. Examples of such oversight committees include:

- Obesity Research Institute Advisory Group
- Kidney Research Institute Advisory Group
- Precision Health Participant Advisory Board
- Precision Health Adolescent Advisory Council

For additional insight into Geisinger's commitment to engaging our community in all aspects of learning and discovery, please see https://www.geisinger.edu/research/get-involved.

Section 21 - Emergency/Disaster Preparedness for Geisinger HRPP and Investigators Conducting Human Research

To ensure sustainability of the HRPP and ensure the rights and welfare of research participants are protected in times of disaster or emergencies, Geisinger HRPP has developed a risk-based emergency preparedness and response plan. While we cannot predict if and when disasters might occur, understanding expectations and permitted flexibilities in HRPP functions and investigator responsibilities ahead of an emergent situation will facilitate adaptable processes that prioritize the safety, rights, and welfare of research participants in such situations (e.g., infectious pandemics, natural or manmade disasters).

Role of HRPP Leadership

Geisinger HRPP organizational structure provides direct access to Geisinger system leadership, who direct the organizational response to disasters and emergencies. In addition, IRB Director, IRB Operations & HRPP as well as those within the Research hierarchy (while at different levels) are members of Geisinger system leadership. In the event of an emergency or disaster, Geisinger system leadership in collaboration with system stakeholders evaluates the situation, initiates, and communicates a response to the situation. The IRB response is driven by organizational and research leadership directives and guidance as well as any regulatory guidance related to conduct of human subjects' research in such situations.

- IRB Director (Director, IRB Operations & HRPP) (or IRB Analyst Lead if Director unavailable) connects with Research Leadership (VP, Research, Chief Scientific Officer, Chief Academic Officer, and/or Institutional Official) to understand the situation (i.e., nature and scope of disaster) and its impact on and expectations for IRB staff, Investigators and staff and continuance of human subjects research.
- IRB Director collaborates with IRB Chair(s), IRB Leadership Committee and Research leadership to determine and develop appropriate specific risk-based response to the emergency/disaster's potential impact of the oversight and conduct of human subjects' research.
- IRB Director communicates response plans (e.g., guidance, expectations, FAQs) to IRB staff and members and collaborates with Research leadership to determine best way to communicate information to researchers and staff (e.g., system announcements via iRIS email to all active users, Research Teams Channel, OurGeisinger Research SharePoint site) as necessary dependent on impact to Geisinger personnel, systems and processes and the scope and severity of the emergency/disaster.
- If appropriate, Research leadership will create ad hoc committees applicable to the situation, for example:
    - Research prioritization oversight committee
        - Membership with representation appropriate to the situation appointed by Research leadership (e.g., research faculty, research operations, clinicians, bioethics, IRB)
        - Provides mechanism for submission of requests for initiating new human subjects' research
        - Systematically reviews, prioritizes, and approves requests for initiating research
        - Communicates determinations to investigator
        - Investigator must attach committee approval to IRB submission

- Research Start/Re-start committee
  - Membership with representation appropriate to the situation appointed by Research leadership (e.g., research leadership, research faculty, research operations, IRB)
  - Provides mechanism for submission of requests for starting (or restarting if research is paused) new human subjects' research
  - Systematically reviews, prioritizes, and approves requests for starting or restarting human subjects research, considering availability and capacity of required resources to conduct research activities (e.g., clinical services, research staff), safety and welfare of research participants
  - Communicates determinations to investigator
  - Investigator must attach committee approval to IRB submission requesting approval to start or resume research activities (e.g., in-person interactions)

Annually, Director, IRB Operations and HRPP will review and update this plan, as applicable

Geisinger HRPP/IRB Functions to Support Human Subjects Research during Emergency/Disaster

Geisinger IRB uses iRIS for life-cycle processing and maintenance of all IRB submissions and communications with researchers and staff. iRIS is an electronic, web-based, IRB system that is locally maintained in an on-premises data center.

Geisinger IRB staff perform work either remotely, hybrid or in office. Regardless of usual work location, all staff have capacity and resources provided by Geisinger to work remotely with full access to all IRB files via iRIS and Geisinger network. In addition, all IRB meetings are virtual via MS Teams and all IRB members have full access to all study files via iRIS.

Per Geisinger policy, Application and Data Criticality Analysis, the Information Technology Department must periodically prepare or revise an assessment of the degree of criticality on all production information systems. This rating be used for contingency planning to include disaster recovery planning and procedures, data backup plans, etc. iRIS is included in Geisinger's annual business criticality review:

- iRIS is rated as "medium," meaning system use *can be deferred 4 to 7 business days before having severe clinical or financial impact*
- iRIS has a Disaster Recovery Plan maintained by Information Technology for use to restore system functioning in the event of disaster.

Depending on the impact on systems such as iRIS or internet, other methods for IRB review and communication might need to be employed based (e.g., paper submissions or documentation that can later be scanned into iRIS, IRB meeting held via telephone). In the event Geisinger IRB staff or committee cannot function and IRB review/oversight is imminently required, Geisinger will consider relying on an external IRB. Geisinger is a SMART IRB participating institution, providing the opportunity to expeditiously facilitate reliance on another AAHRPP-accredited IRB also participating in SMART IRB.

Role of Investigators and Study Staff during Emergency/Disaster

Investigators conducting human subjects research are expected to comply with all institutional guidelines and restrictions related to any emergencies and/or disasters. In doing so, investigators must consider the impact of an emergency/disaster (e.g., infectious pandemics, natural or manmade disasters) on the ability to conduct research and prioritize the safety, rights, and welfare of research participants in such situations.

In general, investigators and research staff should follow directives and guidance provided by Geisinger operations, Research and HRPP leadership. Investigators are not required to submit changes in research conduct related to these system directives to the IRB for review and approval prior to implementation.

Investigators should consider whether a mitigation plan for their research is needed. This might not be necessary if:

- Research does not involve in-person interaction with research subjects.
- Research can be conducted as written while adhering to additional institution-level and IRB guidance and requirements regarding the emergency/disaster event.
- The research is externally sponsored, and the sponsor has developed a protocol-specific risk mitigation plan for the research.
- The research has been voluntarily placed on hold for recruitment and all research procedures (except for necessary follow-up procedures to be done consistently with additional institution and IRB guidance and requirements regarding the emergency/disaster event).
    - Investigators may voluntarily elect to place all recruitment, enrollment, and research procedures on temporary hold during emergency/disaster scenarios if doing so will better ensure the safety of research subjects and would not create any additional risks to the safety and welfare of research subjects. Such voluntary holds on research activity do not require IRB notification or review.

Investigators must submit study-specific emergency/disaster mitigation plans to the IRB for review and approval via IRB amendment/modification submission prior to implementation of the plan.

If immediate changes to the research protocol are necessary to eliminate immediate hazards or to protect the life and well-being of research participants, investigators can implement the change without prior IRB review and approval but must notify the IRB within five business days via IRB amendment/modification form. Investigators should contact IRB staff with any questions related to these requirements.

For all other study modifications made to ensure the ongoing safety of research subjects during emergency/disaster scenarios, submit a study amendment and all relevant new or modified study materials to the IRB via amendment/modification submission.

Communication and Education of Emergency/Disaster Response Plans for Researchers

During emergencies and disasters, investigators and research teams will be promptly notified about activation of response plans through a variety of different mechanisms. These mechanisms may include, but are not limited to, system-wide announcements sent via email, postings on the Research Teams Channel as well as OurGeisinger Research SharePoint website, IRB SharePoint site and/or external Human

Research Protection Program site. Notifications may also be sent out to all active iRIS users and leadership may set-up research wide meetings and town halls to further communicate the activation of any response plans. Research leadership will ultimately decide the best mechanisms to communicate the information to investigators.

IRB staff will coordinate with research leadership and organizational officials in the development and implementation of training materials related to emergency/disaster response plans specific to human research conducted at the organization. The plan and resources will be made available to the research community via posting on the Research Teams Channel, OurGeisinger Research SharePoint website, IRB SharePoint site and/or external Human Research Protection Program site. Training mechanisms may include in-person meetings, town halls, or seminars. Trainings may also be recorded and posted to ensure continued access to information. Training materials may include things like Power Point presentation, information sheets, frequently asked questions, fast facts, check lists, or investigator's guides. The Director, IRB Operations & HRPP and research leadership will ultimately decide the best format and presentation mechanism given the scope and limitations of the disaster and/or emergency and will adapt them based upon the ongoing and changing needs of the institution. They will also be responsible for periodically reviewing and updating educational materials when appropriate.

While training and education will be geared towards both investigators and research staff, principle investigators are responsible for ensuring that all members of their research team are informed and educated about any emergency preparedness plans and adhere to them accordingly. It is expected that all investigators will make viable attempts to attend either live training and education sessions or view the recordings if this mechanism is used. Investigators should communicate to the IRB and research leadership if they are unable to attend a live training session and require an individualized session. Ultimately, Investigators are responsible for ensuring that they understand and comply with all requirements of response plans. Investigators are expected to contact either IRB staff or Research leadership if they are unclear on any plan details or have a situation they feel is not covered by the implemented plan.

Appendices

Delegation of HRPP Authority Letter

April 13, 2022

Julie Byerley, MD, MPH
Executive Vice President/ Chief Academic Officer
Institutional Official
Geisinger
525 Pine Street/ MC 73-00
Scranton, PA 18509
570-504-9620
Jbyerley1@som.geisinger.edu

RE: Delegation of Authority for the Human Research Protection Program (HRPP)

I hereby delegate authority and responsibility to the Executive Vice President/Chief Academic Officer (EVP/CAO) in her role as Institutional Official (IO) for ensuring that Geisinger's Human Research Protection Program (HRPP) functions effectively and that the institution provides the resources and support necessary to comply with all requirements applicable to research involving human subjects. The Institutional Official represents Geisinger Clinic and all Geisinger components named in Geisinger's Federalwide Assurance (FWA00000063).

This delegation includes but is not limited to:

1. Oversight of the HRPP, including Geisinger Office of Research Compliance (ORC), Institutional Review Board (IRB), including appointment of IRB Chairs and members.
2. Oversight of research policies and procedures related to human subjects research.
3. Appointment of panels or advisory groups as needed for HRPP oversight.
4. Maintain open channels of communication between all the components of the HRPP.
5. Oversight of research investigators and staff, administration, and research management.
6. Ensure independence of the IRB, including the authority to act without undue influence.
7. Periodic reviews of the HRPP to ensure that the HRPP is functional, adequately staffed and funded, and respected in the research community.

This delegation shall continue in effect until revised or terminated by me or my successors.

Sincerely,

Jaewon Ryu, MD, JD
President and Chief Executive Officer

CC: Christa Martin, Chief Scientific Officer; Candice Laubach, Vice President, Research; Debra Henninger, Director, IRB Operations and HRPP

Charge to the IRB Members

GENERAL CHARGE:

Geisinger Institutional Review Board (IRB) Members are assigned the authority and responsibility to perform, in an independent and autonomous manner, the key functions of the Human Research Protection Program (HRPP) of Geisinger Clinic and its components named in Geisinger's Federalwide Assurance (FWA) and affiliates. Some functions are described in this General Charge; however, a full description of Geisinger IRB duties and responsibilities is contained in the HRPP Handbook. The primary function of theIRB is the prospective and continuing review and approval of all Geisinger human subject research. The objective of the IRB is to ensure the rights and welfare of research participants are adequately protected andthat all activities involving human subjects are in compliance with applicable Geisinger policies and external regulations.

The IRB is assigned the authority and responsibility for reviewing research involving human subjects (as defined below and in Section 1 of the HRPP Handbook) conducted at Geisinger facilities or by Geisingeremployees, faculty or visiting scientists at any location. This includes the authority to observe the informedconsent process and all aspects of the conduct of the research. All protocols that involve human subjects shall be reviewed at intervals appropriate to the degree of risk and in compliance with federal human subjects research regulations. The IRB may approve research protocols with or without modifications or may withhold approval of all or any portion of a protocol.

The IRB is responsible for the review of all suspected or alleged protocol violations, participant complaints, potential violations, potential non-compliance, and unanticipated problems that increase risk to research participants, as outlined in Section 3 of the HRPP Handbook. The IRB has the authority to take action basedon their reviews, including the authority to suspend or terminate a protocol or an investigator's privilege to conduct human subject research, as outlined in Section 9 of the HRPP Handbook. In cases of suspension or termination, the IRB will immediately notify the affected investigator(s), the Division Chair and/or Department Director, the Institutional Official (IO), and others as required by the HRPP Handbook, Geisinger policies and external regulations (e.g., Food and Drug Administration (FDA), Human Health Services (HHS), etc.).

Upon request, the IRB shall review and comment on proposed external regulations dealing with human subjects research. When appropriate, HRPP staff will formulate draft policies and procedures for approvalby the Institutional Official (IO).

DEFINITIONS:

Department of Health and Human Services (DHHS) Regulations (45CFR46):

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

1) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, oranalyzes the information or biospecimens; or
2) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

Research: 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 part, the following activities are deemed not to be research:

(1) Scholarly and journalistic activities (*e.g.,* oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.

(2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an eventor crisis that threatens public health (including natural or man-made disasters).

(3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activitiesauthorized by law or court order solely for criminal justice or criminal investigative purposes.

(4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security,defense, or other national security missions.

Food and Drug Administration (FDA) Regulations (21CFR50&56):

Human subject: An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

Clinical investigation: 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 21 CFR 58, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of the FDA.

GUIDELINES

The HRPP Handbook describes IRB responsibilities, briefly summarized below:

1. Research shall be reviewed in such a manner as to provide for the protection of participants against lossof privacy and confidentiality, disrespect for human dignity, and physical, psychological, financial or social harm.

2. Conflict of Interest
    a. Human subject research protocols shall be reviewed for potential conflicts of interest involving possible financial gain from research results versus obligations to human participants. This review process is outlined in Section 3 of the HRPP Handbook.
    b. Under the Common Rule (45 CFR 46.107(e); 21 CFR 56.107 (e): "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." The standards for determining if a potential conflict exists and the steps taken if it does are set out in Section 6 ofthe HRPP Handbook.

3. All research protocols involving human participants shall be available for review by any member of the IRB. Any member of the IRB may request convened IRB review of such protocols. Approval of greater than minimal risk research or FDA-regulated research may be granted for no more than one year (365 days); however, appropriate to the degree of risk. Except for life-threatening emergencies and protocolsqualifying for expedited or exempt review, all protocols must be approved at a convened meeting with a quorum (i.e., a

majority of the voting members, including at least one member whose primary concerns are in non-scientific areas and one member whose primary concerns are scientific areas) and affirmativevote of a majority of those present. The IRB review process and requirements are discussed in Section 7of the HRPP Handbook.

APPEALS:

In cases of dispute with respect to procedures or decisions of the IRB, appeals may be made to the IRBChairs or Director, IRB & HRPP Operations. The details and process for such an appeal are set forth in Section 6 of the HRPP Handbook. As this document makes clear, neither Geisinger's Institutional Official, nor Chief Executive Officer (CEO), nor any other Geisinger official or committee may approvea protocol that has not been approved by the decision of the IRB, nor apply undue pressure on the IRBto reverse a decision (as further provided in Section 3 of the HRPP Handbook).

MEMBERSHIP:

IRB members are appointed by the IRB Chairs with input from the Institutional Official (IO) and Director, IRB & HRPP Operations, as applicable. The membership includes at least five members: at least one member whose primary concerns are non-scientific, at least one member from the local community who isnot otherwise affiliated with Geisinger (unaffiliated), at least one member whose primary concerns are backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.

Non-voting ex officio IRB members may include but are not limited to representatives of the Center forTranslational Bioethics & Health Care Policy. Membership is explained in Section 6 of the HRPP Handbook.

IRB member terms are generally for one year and are renewable, beginning January 1 through December 31.

REPORTING OBLIGATIONS:

The IRB reports up through Geisinger's Institutional Official (IO), who is responsible for providingoversight of the HRPP to ensure compliance with federal, state and local regulations and institutional policies governing human subjects research.

MEETINGS:

The IRB meetings are held the first and third Thursday of each month at 2:30 pm.

STAFF SUPPORT:

Geisinger's Institutional Official shall ensure necessary staffing and administrative assistance for theIRB through Geisinger’s IRB Office.

_____ _____

Julie Byerley, MD, MPH Date

President and Dean, Geisinger Commonwealth School of Medicine

Executive Vice President and Chief Academic Officer, Geisinger

Institutional Official, Geisinger

Principal Investigator or Program Director Status

PURPOSE

A principal investigator (PI) or program director (PD) (terms may be used interchangeably) is the single individual who bears responsibility for all aspects of a research or non-research project. This same broad responsibility applies in instances where a project also has a co-PI/PD recognized by a sponsor. Specifically, those who wish to be co-principal investigators (Co-PI/PD's) must meet the same criteria as PI/PD's.

In addition to providing intellectual leadership, the principal investigator accepts overall responsibility for directing the project, the financial oversight of the award's funding, as well as compliance with relevant Geisinger policies and sponsor terms and conditions of an award.

Serving as PI/PD implies acceptance of a variety of roles and responsibilities as bearing full responsibility for the conduct of all aspects of a study, including that delegated to staff or collaborators (i.e. co-PI or co-investigators).

The following institutional policy describes who may serve as PI on proposals to internal or external funding agencies or on projects overseen by various regulatory groups. This policy sets the base institutional policy. It is important to note, however, that external agencies or internal groups such as the Clinic Research Fund (CRF), Institutional Review Board (IRB), Institutional Biosafety Committee (IBC), or Institutional Animal Care and Use Committee (IACUC) may have differing requirements for PI/PD status or that certain projects may require specific expertise or experience.

POLICY

The PI/PD ensures that a project is conducted with the highest standards of responsible conduct of research and stewardship of research funds NOTE: internal or external, especially when a project involves one of more regulated research resources e.g. human subjects, biohazards, radiation or animals and/or involves external sponsorship for the project. In recognition of the considerable and essential responsibilities, a Geisinger PI must meet the following criteria:

Employed, permanent Medical, Nursing, Allied Health Professionals and Research/Scientific staff:
PI status is conferred upon Geisinger-employed permanent Medical, Nursing and Allied Health professionals with terminal degrees (MD, DO, PhD, DNP, PharmD, DPT, etc.) by virtue of their appointment at Geisinger. Requirements for trainees (e.g., residents, clinical fellows, postdoctoral fellows) are addressed below.

Temporary, employed professional staff:
Temporary professional staff locum tenens may serve as PI/PD on non-therapeutic/minimal risk studies. Temporary staff may serve as PI/PD on a study with therapeutic intent or more than minimal risk only if an appropriate member of the permanent professional staff serves as a sub-investigator or co-investigator.

Non-employed physicians:

Non-Geisinger-employed professional staff with Geisinger privileges may serve as PI/PD if the following requirements are met: 1) agree to provide follow-up for subjects and meet the contractual requirements, regardless of whether they maintain privileges with Geisinger; 2) receive Geisinger IRB approval or that of the Geisinger IRB's delegated IRB (e.g., WIRB, CIRB, Wright Center, HMORN, etc.); 3) allow Geisinger to negotiate agreements with outside entities, and assist in these negotiations as necessary; 4) participate in sponsor or regulatory audits; 5) maintain records for as long as specified by contract or regulation; 6) and help Geisinger fulfill its contractual obligations.

Nursing Staff:
Members of the nursing staff without doctorates may serve as a PI/PD upon request made by the nursing service line or department and upon approval by the System VP of Nursing Research. The PI Status Request Letter should be sent to the System VP of Nursing Research for approval; along with the individual/requestor's CV/biosketch and draft protocol or abstract. The protocol must also be submitted and approved by the Nursing Research Council. The signed PI Request Letter indicating approval should accompany the Nursing Research Council approval letter with the study submission to the IRB or any request for funding. (See attached ' Nursing PI Status Request Letter; Nursing Research Council on InfoWeb)

Allied Health Professionals:
Allied Health Professionals without doctorates (e.g., respiratory therapists, perfusionists, physical therapists, occupational therapists, pharmacists, radiology technicians, medical technicians, etc.) may serve as PI/PD upon request by the appropriate service line or department director and upon approval by the Chief Administrative Officer, Research. Approval to serve as a PI may be granted for a specific protocol or proposal or for a range or group of protocols or abstract. The PI Status Request email, along with the individual's CV/biosketch and draft protocol or abstract, should be sent to the Associate Chief Research Officer for his/her signature of approval. This email approval should accompany study submission to the IRB or any request for funding.

Research Staff:
Research faculty members with the title of Assistant Professor or Assistant Professor, Clinical Research, Associate Professor or
Associate Professor, Clinical Research, or Professor or Professor, Clinical Research, and who meet the criteria to submit an
Institutional Review protocol, may serve as PI/PD. Other research staff without doctorates or investigator titles (Biostatisticians, Staff Scientist, Bioinformatics Scientist, Instructor etc.) may serve as PI/PD upon request made by the appropriate service line, department or center director/chair and upon approval by the Chief Administrative Officer, Research. Approval to serve as a PI may be granted for a specific protocol or proposal/project specifics basis. The PI Status Request email, along with the individual's CV/biosketch and draft protocol or abstract, should be sent to the Chief Administrative Officer, Research for his/her signature of approval. Please provide as much information about the request as possible. Email approval should accompany study submission to the IRB or any request for funding.

If you are unsure if you require CAO approval to be a PI/PD, please email researchgrants@geisinger.edu or grantsupport@geisinger.edu for clarification.

Trainees:
Residents, clinical fellows, postdoctoral fellows, graduate students and other trainees may not serve as PI/PD. In instances where funding is specifically designed to support individual graduate students, postdoctoral or medical fellows (cumulatively 'trainees') and requires the trainee to serve as the Principal Investigator, the trainee may serve as PI/PD. Email approval from the Chief
Administrative Officer, Research must accompany all grant/contract proposals or submissions. Internally at Geisinger, the trainee will serve as a sub-investigator and the trainee's mentor will serve as PI/PD of the project and will be considered the individual responsible for the management of the project and the award and must meet the criteria to serve in this role as outlined in this document.

Senior Administrative Staff (Executives, Vice Presidents, Directors):
Senior Administrative Staff may serve as PI/PD on non-research proposals in their area of responsibility. Those with appropriate research training (as evidenced by a MD, PhD, or other terminal degree) may serve as PI/PD on research projects consistent with the section above on Employed, permanent Medical and Scientific staff.

Other:
Individuals not addressed above may serve as PI/PD upon request made by the appropriate service line, department or center director and upon approval by the Chief Administrative Officer, Research. Approval to serve as a PI may be granted for a specific protocol or proposal or for a range or group of protocols or proposals. The PI Status Request email, along with the individual's CV/biosketch and draft protocol or abstract, should be sent to the Chief Administrative Officer, Research for his/her signature of approval. This email approval should accompany study submission to the IRB or any request for funding.

Additional Criteria that May Apply

1. Individuals with PI/PD status may serve as PI on proposals submitted to outside funding agencies in support of research, training, program or other sponsored activities. They may also serve as PI/PD on IRB, IACUC, and IBC protocols and radiation licenses. However, if external sponsors, regulatory committees, departments or divisions have more restrictive policies for PI status, these requirements must be observed.
2. Serving as a PI is a privilege. PI's must complete all required training. The right to serve as a PI may be withdrawn or temporarily suspended if the requirements of the internal funding body, regulatory committees, or external sponsors are not met.

Investigational Drugs

PURPOSE

To protect the safety of patients participating in investigational or clinical medication studies by providing a process for the safe and appropriate use of investigational drugs within the Geisinger Health (GH).

POLICY

1. Investigational Drugs will be controlled and administered in compliance with standards of all relevant regulatory agencies
2. A summary or copy of the Institutional Review Board (IRB) approved protocol, a copy of the signed informed consent, and data pertinent to safe administration of the investigational drug(s) will be made available to any patient care area administering investigational drugs.
3. Protocols and informed consent forms must be kept current. Any revisions to the protocol or the consent must be provided to the patient care area when they are made.
4. Any use of an investigational drug or non-FDA approved drug not specifically defined in this policy (i.e., single patient use, treatment use or parallel track use) requires consultation with the GH IRB and the Investigational Drug Pharmacy.

DEFINITIONS

1. **Authorized Prescriber:** An authorized prescriber is a provider who is authorized to prescribe the investigational drug(s) as a Principal Investigator (PI) or Sub-Investigator.
2. **Emergency Use of an Investigational Drug:** The use of an Investigational Drug outside of a GH IRB-approved protocol with a human subject in a life-threatening situation in which no standard acceptable treatment is available an in which there is not sufficient time to obtain GH IRB approval.
3. **Investigational Drug:** A chemical or biological drug that is being studied in a clinical trial. It can be either 1) an Investigational New Drug, or 2) a Federal Drug Administration (FDA) approved drug being used under and IRB approved protocol for human research, possibly outside of FDA-approved labeling. Any concurrent medications, comparators, or rescue medications used in an Investigational Drug protocol that are not the drug(s) being studied will be handled as Investigational drugs if necessary, for tracking purposes as specified in the study protocol.
4. **Investigational New Drug:** Investigational drugs are defined as those that are being considered but have not yet received marketing approval by the Food and Drug Administration for human use and those drugs that have FDA approval for at least one indication but are being studied in an Institutional Review Board (IRB)-approved research protocol for new indications, new routes of administration, or new dosage forms

PROCEDURE

1. Any protocol involving the administration of an investigational drug or investigational new drug to human research subjects must have, as a condition of approval, an IDS Authorization Number from the IDS Pharmacy. This Authorization Number provides the IRB with evidence that a drug review has been performed for the protocol, including any potential impact on the IDS Pharmacy; dosing issues; reimbursement issues; assessment of clinic staff's knowledge of proper drug storage, labeling, record-keeping, security, etc.; assessment of the site's ability to meet these requirements; and determination of the IDS Pharmacy's role, if any. As part of this process, the PI (or designee) will supply to the IDS Pharmacy the current copy of the protocol and Investigator's Drug Brochure(s) (if applicable). Prior to dispensing any investigational drug as part of a clinical research protocol, the IDS Pharmacy must have the IRB approval letter, FDA 1572 (when applicable) and documentation of informed consent on file.
    a. For any GH IRB-approved INPATIENT study: Any GH IRB-approved protocol involving the administration of an investigational drug or investigational new drug to a research subject as an inpatient MUST use the IDS Pharmacy.
    b. For OUTPATIENT Studies, the clinic may handle its own medications if the following requirements are met. If not, the IDS Pharmacy will assist with the trial.
        i. Medications are stored in a LOCKED room or cabinet accessible ONLY to study personnel.
        ii. Medications are stored at the proper temperature.
        iii. There are no non-study medications, samples, or food items in that location. iv. USED medications are kept separate and under the same security conditions.
        iv. All medications leaving the clinic with subjects will be labeled with the CLINIC name, INVESTIGATOR name, 24-hour PHONE NUMBER, and CLEAR directions.

2. Inpatient and Outpatient use of Investigational drugs for GH IRB-Approved protocols: dispensed by the GH Investigational Drug Pharmacy:
    a. The Principle Investigator, or designee, will provide a summary or copy of the IRB approved protocol and a copy of the signed consent to the patient care area. Unit staff should receive education and/or training about the study protocol as it pertains to their role(s) in the study.
    b. All orders and prescriptions to initiate, modify, and discontinue treatment with an Investigational Drug must be signed by an authorized prescriber (either hand-written or electronically).
        i. Authorized prescribers may be verified by several means:
            1. FDA Form 1572 (when applicable)
            2. Geisinger's NCI Authorized Investigator list (see attachment)
            3. Geisinger's IRB application for the study in question
    c. Storage of Investigational Drugs by the Investigational Drug Service (IDS) Pharmacy:

i. Investigational drugs will be stored according to the label requirements. ii. Refer to the Temperature / Humidity Monitoring policy (#10001602)

iii. For locations with an IDS-specific TempTrak sensor/transmitter, the temperature range for alarms will be as follows:

1. Refrigerator: 37F-45F – Immediate alarm
2. Room Temperature: 60F-85F – Immediate alarm iv. In the event of a temperature excursion, refer to the investigational drug protocol documents (Protocol, pharmacy manual, etc.) and follow the instructions. If there is no temperature deviation information, quarantine the affected investigational drug(s) ad contact the study monitor/sponsor for guidance.

d. Dispensing of Investigational Drugs by the Investigational Drug Service (IDS) Pharmacy:

i. In addition to all generally required label information, the IDS Pharmacy will label all investigational drugs with the words 'Caution: New drug limited by federal law to investigational use.

ii. The electronic investigational Drug Accountability System (IDAS) (Vestigo) will be used to document all accountability activities, unless otherwise directed.

e. Administration of Investigational Drugs:

i. Administering staff will review unit-based drug information prior to administration.

ii. **Note:** Contact the Investigational Drug Pharmacy if there are questions about the safe use of any Investigational Drug.

i. Return of Investigational Drugs:

i. Return any unused Investigational Drugs dispensed by the IDS Pharmacy that are not administered.

ii. **Note:** Partially used or empty containers for Investigational Drugs that are potentially hazardous (i.e., because they contain sharps, cytotoxic, or infectious materials) should not be returned to the IDS Pharmacy and should be disposed of according to the institution's policies and procedures for regulated medical waste.

ii. Transportation of Investigational Drugs: Refer to the attached procedure

3. Inpatient and Outpatient Use of Investigational Drugs from GH IRB-Approved outpatient protocols that are not dispensed by the GH IDS Pharmacy:

a. The Principal Investigator, or designee, will provide a summary or copy of the IRB approved protocol and a copy of the signed consent to the patient care area. Unit staff should receive education and/or training about the study protocol as it pertains to their role(s) in the study.

b. For outpatient study drug(s) not dispensed by the IDS Pharmacy, the PI is required to follow the IDS Pharmacy-approved provisions for dispensing to outpatients.

c. Inpatient use of Investigational Drugs from GH IRB-Approved outpatient protocols not dispensed by the GH IDS Pharmacy will be handled according to the GH policy Medication

Management: Home Medication Management and will not be dispensed from the GH IDS Pharmacy.

4. Inpatient use of Investigational Drugs dispensed from other institutions:
   a. Investigational drugs from other institutions will be handled according to the GH Medication Management: Home Medication Management) and will not be dispensed from the GH IDS Pharmacy.
   b. The GH attending physician, or a designee will contact the other institution to assure that the patient is appropriately followed and to obtain all relevant information regarding the investigational drug, its effects, contraindications, drug interactions, and other pertinent data required for safe administration as part of the medication reconciliation process.
   The GH attending physician or designee will obtain a summary or copy of the approved protocol and place it in the patient's medical record.
   c. The GH attending physician or designee will obtain a summary or copy of the signed informed consent and place it in the patient's medical record.
   d. The GH attending physician or designee will provide the patient care area with the above investigational drug information prior to placing an order for the use of a patient's own medication from home.

5. Emergency Use of an Investigational Drug outside of an IRB-approved protocol:
   a. The Principal Investigator (PI) will notify the IDS Pharmacy of the intent to use the Investigational Drug and arrange for shipping of emergency supply of the drug directly to the IDS Pharmacy with any pertinent information regarding the safe and effective use and preparation of the drug.
   b. The PI will obtain informed consent from the patient or his/her surrogate decision maker according to IRB requirements.
   c. The PI will notify the IRB of the use of the investigational drug according to the IRB requirements

Payments to Study Participants

PURPOSE

The purpose of this policy is to establish uniform guidelines for the management and disbursement of payments to study participants.

POLICY

Geisinger requires approval from the Institutional Review Board (IRB) for any payment to study participants. Each Center/Department will implement proper controls to account for all funds disbursed to study participants. All payments discussed in this policy are subject to requirements established by the Internal Revenue Service (IRS), which requires that all payments to individuals, including payments to research subjects, be reported using an IRS 1099 form if they equal or exceed the current IRS reporting threshold.

DEFINITIONS

Form 1099: official form used by the Internal Revenue Service used to report various types of income other than wages.

RESPONSIBILITIES

Principal Investigator

- The Principal Investigator is ultimately responsible for all funds disbursed under this policy, however, he/she can delegate the custodial functions of the funds to the Study Team member.

PI or Study Team member

- For gift cards, maintain an inventory listing of all cards and keep this list in a separate location from the cards.
- For gift cards issued to Geisinger employees, email the Payroll Office (payroll@geisinger.edu) the employee's name, Lawson ID and value of the gift card. Maintain a study log. The log must include the date, participant name or ID, study IRB number, and the value of the card.
- Store gift cards or cash in a locked area.
- Provide Research Finance with a Study Participant Account Reconciliation form within thirty days of the termination of the project.
- Reimburse the project immediately for any unused gift cards or funds.

Research Finance

- Review the Study Participant Account Reconciliation and contact the Program Manager if there are any unresolved balances or variances.

- Close out the project in accordance with the Award Closeout policy.

Financial Reporting

- Audit of Petty Cash Funds: Financial Reporting can conduct random audits of the Petty Cash Fund. Petty Cash will be counted by the Financial Reporting staff in front of the location's cash custodian or manager. Financial Reporting verifies the current receipts/vouchers and remaining cash. The custodian and manager will sign to acknowledge that the Petty Cash Fund was audited. Each entity determines the frequency and type of audit of petty cash funds. Financial Reporting can audit the fund or the department can perform a self-audit. A self-audit by the custodian should be done at each replenishment request. Management should audit the fund at the time of any custodian change. Annually, Financial Reporting sends the self-audit materials for Petty Cash. Acknowledgement of this audit requires signature from the manager.

Non-compliance with the policy will be subject to disciplinary action up to and including termination.

PROCEDURE

Payments to study participants can be made by checks, gift cards, or cash. Payments to participants cannot be used by the participants to offset any outstanding receivable balance they may have with Geisinger.

Checks through Accounts Payable. Geisinger prefers the use of Geisinger checks when compensating study participants. A Request for Payment with a description of the check request and the IRB protocol number is completed for each participant. Payment by check is subject to the IRS reporting requirements. This method cannot be used if the identity of the study participants is to be kept anonymous.

Payment by gift cards. The distribution of gift cards to research subjects in exchange for participation in a research study is allowable. Gift cards are considered 'cash or cash equivalents' and are subject to Geisinger's expenditure guidelines. Gift cards are monetary in nature and subject to the IRS reporting requirements. Gift cards can only be used on projects where the total amount paid to each participant by that project does not exceed $100.

Payment by cash. Cash payments can only be made if the study requirements do not allow other payment methods or the payment per participant is a low dollar amount (eg awarding children $1 upon successful completion of a research question/task). Cash payments are subject to IRS reporting. **Geisinger Employee participants.** The value of cash payments or gift cards issued to employees must be reported to the Payroll Office. An email including the employee's name, Lawson ID and value of the gift card should be sent to payroll@geisinger.edu .

Controls

Regardless of the payment method listed above, the department/center will implement controls to safeguard the funds. The controls must include the following:

- All payments by cash or gift cards are subject to Geisinger's Petty Cash Fund policy and must be monitored routinely.
- For gift cards, an inventory log of all cards, must be maintained. The log must list the card numbers along with all receipts, withdrawals, and balances of cards. This listing must be kept in a separate location from the actual cards.
- Withdrawals of cards require a dual signature on the inventory log.

- A study log must be maintained for each project, identifying the project name, Activity code, IRB protocol number, transaction date, study participants and payments made to them.
- Gift cards may be purchased through the following:
    - Purchase with a Concur Card and reconciled monthly (physical card or electronic by e-mail).
    - In the case of international gift card purchases, a personal credit card can be used and then seek personal reimbursement through Concur.
- The use of generic gift cards is encouraged. Imprinted holiday, animal, and other themes are not allowed.
- All expenses must be processed in compliance with the Travel and Business Expense Policy and the Corporate Card Policy.
- The PI/designee will determine the number of cards needed and the length of the study. The number of cards purchased with sponsored funds must be kept to a minimum to cover the immediate needs. It is recommended that this quantity does not exceed one month's supply of gift cards needed for the study.
- At the end of a study, the cost of any unused gift cards will be transferred to the home unit and the cost of the gift cards will be reimbursed by the home unit to the sponsored project. Unused cards that are transferred to the home accounting unit are still property of Geisinger and can only be used to fund normal operating expenses (such as supplies) in accordance with the department's operating budget. The department must maintain a log of all cards and is subject to random audits. When unused gift cards transferred to the home unit cannot be used to fund normal operating expenses (eg. gift cards from restaurants, grocery stores or gas stations), these cards must be donated to a non-Geisinger charity. The cost for these cards must be absorbed by the home unit.
- When gift cards or funds held for study participants cannot be accounted for, the PI or Study Team member will contact the offices of Internal Audit, Research Compliance and Research Finance immediately upon discovery of the missing funds. The PI will be required to provide these offices with a corrective action plan, describing the controls that will be implemented to prevent similar problems from happening again and reimburse the project for the value of the missing cards or funds. Reimbursement cannot be made from other sponsored projects.
- Complete the Study Participant Account Reconciliation Form. This form must be completed as soon as all gift cards have been distributed, but by no later than the closeout of the sponsored project.

Human Research Using Radiation Sources

PURPOSE

To establish a standard approach to the evaluation and approval of research projects which involve the use of radiation sources in or on humans, and comply with regulations which govern human research

POLICY

Regulatory Code:

10 CFR 35.6 (Radioactive Material)

- Licensees may conduct research in human subjects involving radioactive material, provided that the research is conducted, funded, supported, or regulated by another federal agency, which has implemented the federal policy for the Protection of Human Subjects. Otherwise, the licensee must submit an NRC and/or PA State DEP license amendment before conducting the human research.
- The licensee shall obtain informed consent from the human subjects.
- The licensee shall obtain prior review and approval of all activities by the Institutional Review Board and the Radiation Safety Committee.
- The licensee shall comply with all applicable federal and state requirements governing radioactive drugs and devices.

25 A Code Chapter 221.15 (Radiation-producing Machines)

- Registrants who conduct human research using x-rays are exempt from section 221.15 if the research is conducted, funded, supported, or regulated by another federal agency that has implemented the policy for Protection of Human Subjects.
- The research shall be authorized by a committee of at least 3 persons, with one person knowledgeable in radiation effects on humans.
- Research subjects or their legal representatives shall sign a statement acknowledging they were informed of the radiation exposure and possible consequences.
- For projects that do not meet the criteria for exemption stated above, the registrant shall submit a written request for approval to the State and update the information as necessary including the:
    - applicants name and address
    - population to be examined (age, sex, physical condition)
    - known alternate methods not involving ionizing radiation which could achieve the goals of the research program
    - evaluation of the x-ray system by a qualified expert
    - evaluation of individual and cumulative patient exposure

- diagnostic quality control program to be used
- technique chart to be used
- operator and physician qualifications; extent of supervision
- name and address of persons who will interpret the exams
- research protocol

PROCEDURE

Procedure for Radiation Safety Approval:

Human research projects involving radiation are regulated by State or Federal agencies depending on the radiation source. Prior to using radiation in human research, the principal investigator (PI) shall have written project approval from the applicable Radiation Safety Committee(s) and the applicable Institutional Review Board (IRB).

- Persons requesting approval for human research shall complete an IRB application and indicate if the research involves ionizing radiation exposure that is not clinically indicated, where clinically indicated means for diagnosis or treatment considered to be standard medical procedure for the clinical management of the patient.
    - If affirmative, this action will activate a notification to the Chair, Radiation Safety Committee (RSC) and the Radiation Safety Officer (RSO).
- The Human Research RSC Subcommittee, consisting of the RSC Chair, RSO, the general Radiology representative on the RSCs, and one provider from each RSC (minimum of 3 RSC Subcommittee representatives), will review the application and:
    - Approve the application, followed by an informational presentation to each RSC at the next meeting, or ○ Recommend modification that will allow approval by the subcommittee, or ○ Recommend that the application be presented to the full Radiation Safety Committee for review at their next meeting.
- Approval by the Human Research RSC Subcommittee or the Radiation Safety Committee will be based on meeting applicable regulatory requirements; implementation of appropriate radiation safety procedures to minimize radiation exposure / contamination to patients, employees, visitors, and to the surrounding community; and an evaluation of the potential radiation risk.

Research Education and Training Policy

PURPOSE:

The purpose of this policy is to outline the required research educational training requirements for investigators, research staff, and compliance committee members, such as institutional Review Board (IRB) that are necessary to achieve a high level of professional and ethical behavior in the conduct of research at Geisinger.

PERSONS AFFECTED:

This policy applies to all investigators and members of the research staff (including persons not employed by Geisinger but conducting research at a Geisinger entity), non-traditional research personnel (including persons such as students, volunteers or interns), members of the medical staff, compliance committee members, and employees of Geisinger conducting human subjects research.

POLICY:

Geisinger is committed to ensuring high standards of scientific and professional integrity and ethical practices through the implementation of a research educational training program that meets all institutional obligations and complies with all applicable laws and regulations, including any applicable National Institute of Health (NIH) policy requirements.

Training for human subject research must be completed prior to:

- Submitting a new research study application, continuing review or amendment to the IRB
    - Research Determination Worksheet (RDWs) submissions **do not** require research training
- Adding new investigators and research staff to a research study or grant application
- Submitting a research grant application
- Processing a research grant award notice
- Executing of a sponsored research contract
- Reviewing study submissions as an IRB committee member

A training option was developed through the Collaborative Institutional Training Initiative (CITI) for human subjects' researchers and staff. The training includes Human Subjects, Good Clinical Practice (GCP) and Responsible Conduct of Research (RCR) training. All courses are valid for three (3) years from the date of completion. All researchers and staff, including students, must initially complete the Basic Course, in 3 years complete the Refresher Course and then continue rotating between the Basic and Refresher Course every 3 years thereafter. The available training courses include:

- Basic Human Subjects, Researchers & Staff, IRB Members & Staff Required for researchers and staff conducting human subjects research – Modules include:
    - CITI Good Clinical Practice Course
    - Human Subjects & Data Only Researchers & Staff, IRB Members & Staff
    - RCR for Researchers, Research Staff, and Administrators

***Refresher Required in Three years, after which a Basic Course will be required**

Additional didactic RCR training courses are required for all postdoctoral researchers and investigators with the following awards: **D43, D71, F05, F30, F31, F32, F33, F34, F37, F38, K01, K02, K05, K07, K08, K12, K18 K22, K23, K24, K25, K26, K30, K99/R00, KL1, KL2, R25, R36, T15, T32, T34, T35, T36, T37 T90/R90, TL1, TU2, and U2R.** Please check the ORC website for the current didactic training schedule.

External Researchers or Staff Conducting Research at Geisinger

External researchers or staff conducting human subjects research at Geisinger must complete CITI Human Subject Research (HSR) training. Training requirements from their 'home' institution are accepted unless the external researchers or staff have a dual appointment with Geisinger. If so, the staff must comply with Geisinger's training requirements.

External staff must send an e-mail to the Office of Research Compliance (ORC) at orc@geisinger.edu with a copy of the human subjects training certificate attached. The CITI training certificate must include the title of the course, completion date and expiration date. If the certificate lists n/a as the completion date, the certificate will be valid for three (3) years after the completion date per Geisinger CITI training requirements. ORC staff will forward the training certificates to IRB staff to update training in iRIS, electronic IRB system, and upload into the appropriate iRIS user account.

Students, Volunteers, or Interns Conducting Research at Geisinger

Students, volunteers, or interns conducting human subjects research with an investigator at Geisinger or Geisinger affiliate are required to complete Geisinger's Human Subject & Researchers & Staff, IRB Members & Staff courses listed above.

External Researchers and Research Staff Training Exception

If Geisinger researchers and staff are conducting human subjects research under a grant sub-award with another institution and the external site is using Geisinger data, the external researchers or staff **MUST** comply with their home site CITI training requirements and are not required to follow Geisinger's training requirements.

CITI Training course descriptions

- **CITI Good Clinical Practice Course (GCP) –** A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.
- **Human Subject & Data Only Researcher & Staff, IRB Members & Staff, (HSR)** – Includes the historical development of human subjects' protections, as well as current information on regulatory and ethical

issues. This training pertains to all individuals involved in research studies involving human subjects, or who have responsibilities for setting policies and procedures with respect to such research.

- **RCR for Researchers, Research Staff, and Administrators (RCR)** – The practice of scientific investigation and integrity. It involves the awareness and application of established professional norms and ethical principles in the performance of all activities related to scientific research, including conflict of interest (COI) and research misconduct (NIH-NOT-OD-10-019).

If the required CITI research educational training has not been completed or is not current, investigators and research staff cannot be included on a protocol submission to the IRB for review or be included on a research study, grant, or contract submission.

The training is monitored monthly and staff with expired training are notified and given 30 days to complete the training or be removed from the research study. Failure to comply may result in a request to the IRB for study suspension or administrative closure of the study if an exempt study.

DEFINITIONS

External Researchers and Staff: An external investigator or research staff (not employed by Geisinger or a Geisinger affiliate) working with a Geisinger Principal Investigator assisting with conduct or reporting of research.
Human Subject: A living individual about whom an investigator (whether professional or student) conducting research:

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

Investigator: The Principal Investigator or program director and any other Senior/Key Personnel, regardless of title or position, who is responsible for the design, conduct, or reporting of research), regardless of research funding source.
Interns (Paid or Unpaid): Individuals who volunteer for the purposes of education or professional interest as part of a formal or informal educational program.
Research: Any systematic investigation designed to develop or contribute to generalizable knowledge, including all basic, applied and demonstration Research in all fields of knowledge: (a) conducted pursuant to an agreement between Geisinger and a third party; (b) supported by funding that is administered through Geisinger (e.g., through the Office of Sponsored Programs, Research Executive Committee, center, institute, or department; or (c) requiring review by a Geisinger regulatory body (e.g., the Institutional Review Board).
Students: Student (paid or unpaid) who is learning about research under the supervision of a Principal Investigator, while still attending graduate or undergraduate studies at a university.
Volunteer staff: Individuals who volunteer or donate their time or services to a Principal Investigator, usually on part-time basis, without contemplation of pay.

REFERENCES

Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance (1.24)

Update on the Requirement for Instruction in the Responsible Conduct of Research (NOT-OD-019)
https://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-019.html