HRPP HANDBOOK

Table of Contents

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Section 1 - The Human Research Protection Program

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

Geisinger Policy 09.101 Geisinger Human Research Protection 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.

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.

1.1 Organizations Covered by the Geisinger Human Research ProtectionProgram (HRPP)

All Geisinger clinics and hospitals and/or subsidiary entities listed in the Federalwide Assurance are considered part of the organization for purposes of the HRPP and are covered by the HRPP Handbook.

The responsibility for the protection of human participants is shared by several organizational

components that conduct research, as well as those responsible for the program administration of 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 HRPP was established to protect human research participants by ensuring that:

- The rights and welfare of human research participants are adequately protected.
- Human subject 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 levelof expertise and integrity.
- Human subject research complies with all applicable laws, which include local, state, federal, and international laws and regulations.

Objectives of the HRPP

The HRPP establishes 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
- Intervene in human subject research and respond directly to concerns of researchparticipants, when appropriate and necessary.

HRPP Process

The HRPP is comprised of policies, guidance documents, and any other supporting documents governing human subjects research and the protection of participants. The HRPP is approved by the Executive Vice President (EVP)/ Chief Scientific Officer (CSO). For reference in this manual, the EVP/ CSO will be subsequently referred to as the CSO who also serves as the Institutional Official (IO). 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 Chief Scientific Officer (CSO) whose responsibility is to exercise appropriate administrative oversight to ensure thatGeisinger's

policies and procedures designed for protecting the rights and welfare of human participants are effectively applied in compliance with its Federal Wide 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 not a static document and elements may be modified frequently because of scientific developments, ethical issues, and evolving and improving regulatory environment and processes. The HRPP Handbook reflects current practices of the HRPP for IRB review and approval of human subjects research. The Office of the Institutional Review Board (IRB) has been delegated to maintain policies and procedures and oversee the HRPP. Through the Director, IRB Operations and HRPP, IRB staff conduct regular reviews (i.e., at least annually) and refinements of the HRPP Handbook. Recommendations for any modifications or the development of new policies and procedures are made as necessary and appropriate. The CSO 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

*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**)*

Types of human subjects research at Geisinger

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

The Geisinger Institutional Review Board has expertise to review and oversee biomedical (scientific base of information about normal or abnormal physiology and development, and studiesprimarily intended to evaluate the safety, efficacy, and usefulness of drugs, biologics, devices, medical products, procedures or interventions) and behavioral and social sciences (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 expands 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 evaluates 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 the 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 the research;
- Obtaining the informed consent of human subjects for the research.
- 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 finalization of the signed contract 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 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 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:

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

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

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 Researcher appropriately document the consent process. (AAHRPP Element II.3.F)

In some circumstances it may be inappropriate to document consent by using the standard written and signed consent document, and there might be different rules on determining e.g., who may serve as a legally authorized representative (LAR). Refer to Section 12 for information on waivers and alteration of consent, etc.

Additional Requirements

The IRB will review any specific details for federally funded research to be sure that the regulations of that sponsoring agency apply and the required federal protections must be provided; it is not sufficient to provide "equivalent" protections if additional protections are required.

1.5 Primary Officials, Administrative Individuals of the HRPP

Officials Responsible for the HRPP

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

- Creating, establishing and maintaining the policies and procedures for the HRPP and related

research policies and procedures on behalf of Geisinger
- Overseeing the protection of human participants, regulatory compliance, andthe implementation of the HRPP for Geisinger
- Appointment and oversight of ad hoc or advisory committees as needed.
- Ensuring that all components of the HRPP communicate effectively
- Overseeing research investigators and staff, and research management
- Ensuring the independence of the IRB, including the authority to act without undue influence
- Requiring periodic reviews of the HRPP
- Ensuring that 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 CSO delegates day-to-day operational and oversight responsibility to the Director of the IRB Operations and HRPP, who is a full-time administrator and reports to the Chief Administrative Officer, Research.

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

The concept or model of the Learning Healthcare System (LHS) was initiated by the Institute 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 and 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 a 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 of 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 use 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.

Currently, Geisinger's LHS working group includes representatives of clinical operations, administration, research, bioethics and research oversight, quality and safety, clinical innovation, health services research, and academic affairs. The group is a microcosm of a LHS, surfacing issues that will be faced on a larger scale with system-wide operationalization.

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 toward a LHS. 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 success in developing and implementing a revised oversight "system" for discovery has required significant efforts to educate Geisinger staff, especially investigators and research staff, on both the facilitating features and the protections afforded by such a system.

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 of 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. David H. Ledbetter, PhD, is executive vice president (EVP), chief scientific officer (CSO), and institutional official (IO) at Geisinger. Dr. Ledbetter co-chaired the Research Advisory Task Force that created Geisinger's 10-year research strategic plan.

IRB Leadership Committee

The IRB Leadership Committee is comprised of the following: Director of Policy and Education, Chief Bioethics Officer and Associate Directors, IRB Chairs, Director IRB Operations and HRPP. Members of the committee are also members of the LHS plenary group and serve 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 particular 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 CSO officially appoints the IRB chairs. The IRB chairs, after consultation with the Associate Director of IRB, appoint the IRB members. The CSO assigns the authority and responsibility of the chairs 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 coveredorganizations, if needed, to ensure protection for human research participants. The IRB authority, membership requirements, and responsibilities are described in Section 6. 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.

Geisinger contracted with Western IRB (WIRB) for review of all multi-center industry and adult oncology clinical trials from 2006-2011. WIRB will retain the oversight of the industry study clinical trials until study closure.

IRB Staff: The Director, IRB Operations and HRPP is responsible for the daily operations of

the IRBs, and the education program. The IRB staff (Specialists, and Analysts) review study submissions for accuracy and completeness and act as liaisons between the Principal Investigators (PI's) and the IRB members. Each individual area within the HRPP are 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 Geisinger individual ultimately responsible for a protocol is the Principal Investigator (PI). Policy 14.201 – Program Director-Principal Investigator Status outlines who can serve as a PI. PI responsibilities are specified in Section 14 and include ensuring that:

- Geisinger human subjects research receive initial prospective review and approval by the IRB.
- Continuing review and approval of the research has been accomplished within the time frame stipulated by the IRB.
- The research is conducted at all times 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. See Section 14 (Principal Investigator Standards) for detailed responsibilities and duties of research teams.

Sponsors

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

Research Participants

Participants in a research project also have responsibilities. Responsibilities include tellingthe 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 review, discuss, and evaluate new ideas, business relationships, partnerships, collaborations, etc. If any potential institutional

conflicts of interest are identified, the Chief Administrative Officer for Research facilitates review by the Institutional and Research Conflict of Interest Committees. If the ICOIC or RICOC determines that an institutional conflict of interest may exist, the conflict of interest must be managed and minimized or eliminated.

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 as a result 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 all non-research related conflicts ofinterest.

Research Conflict of Interest Committee (RCOIC): A committee established by Geisinger to review research conflict of interest disclosures from all investigators to determine if a potentialconflict of interest exists in current research studies. The RCOIC considers the conflictinginterests, determines or assesses any mitigation or management plan, and determines whetherthe conflict can be managed or needs to be eliminated. If further review is appropriate, the caseis examined by the Chair of the RCOI Committee and consultation with Chief Scientific Officer (CSO) if necessary. A Chair of the IRB is also a member of the RCOIC.

See Policy 14.702 – Geisinger Policy on Financial Conflicts of Interest in Research for reporting details and policy. Section 3.7 also provides additional details.

Institutional 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 in recombinant DNA technology and the capability 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 must be submitted and approved by the IBC 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.

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. All human research studies involving additional use of radioisotopes and lasers must be submitted and approved by the RSC prior to submission and review of the study by the IRB. A copy of the RSC approval letter is uploaded with the study submission to the IRB.

Corporate Compliance Program: The Corporate Compliance Program is enforced by various departments and committees throughout with oversight residing under the Geisinger Board of Directors.

Research Investigative Committee (RIC): The RIC is a committee within Geisinger comprised of leaders in ISO, HIPAA Privacy, ORC, Research Administration, the Department of Legal Services, etc. and is empowered to conduct a preliminary investigation and review of allegations of research non-compliance and/or unanticipated problems involving risks to human

subjects or others. ORC staff provides a report from RIC to the IRB staff for IRB review and final determination.

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 programof patient care, education, research, and community service. ISO performs risk assessments for use and transmission of patient data for research purposes. Any human research study that includes transmission of identifiable data must be reviewed by ISO prior to protocol submission to the IRB. A copy of the ISO notification is uploaded with the study submission 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.

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 and participant protection.

Scientific Review Committee (SRC): The SRC provides peer review of investigator-initiated, more than minimal risk studies if the study was not subjected 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.

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.

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 checked 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 sponsoredprojects. 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.

Research Finance: The responsibilities of Research Finance include the accounting and post

award administration of externally funded research projects and programs at Geisinger. Research Finance reports directly to Geisinger's Vice President Finance/Chief Financial Officer (VP/CFO). 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 allow ability 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 evidence-based nursing practice and nurse-initiated research. The study submission captures whether the study is a nursing based research study. If so, the NRC submission number is captured in the study application as well as a copy of NRC approval letter uploaded with the study submission prior to review and approval by the IRB.

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 Pharmacy number is captured in the study submission to the IRB.

Corporate Communications - Public Relations and Marketing: Corporate 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. Corporate Communications offers public relations, marketing, graphic design and employee communication strategies for Geisinger. Corporate Communications partners with physician leaders, develop comprehensive marketing strategies that include integrated, consistent messaging throughout multiple mediums. Research posters or advertisement within Geisinger must be reviewed by Corporate Communications. A copy of confirmation of the review must be uploaded with the study submission 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" (Belmont Report).

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)

At a minimum, all human subjects research performed under Geisinger HRPP will meet the following requirements:

Respect for Persons

- Research protocols must say how subjects will be recruited.
- Subjects must freely agree to participate after receiving complete information about the research and its risks, potential benefits and alternatives, unless the IRB grants waiver of consent.
- Subjects must fully understand their rights including the right to discontinue at any time without loss of otherwise available benefits, unless the IRB grants waiver of consent.

- Vulnerable populations (fetuses, children, prisoners, those without decisional capacity, and those with economic or educational vulnerability) must receive special consideration and protection.

Minimizing Risks and Avoiding Unreasonable Risks

- Research may not expose subjects to unreasonable risk of harm (whether physical, psychological, social, legal or economic in nature).
- The probability and magnitude of possible harm must be reasonable in relation to the anticipated direct or indirect benefits of participation in any research project.
- Identifiable risks that practicably could be avoided without undermining legitimate research objectives must be eliminated.
- Sound research designs that minimize risks and maximize benefits of participation must be used.

Equitable Recruitment and Selection of Subjects

- Research protocols must promote equitable recruitment and selection of subjects, as applicable, with the overall goal of ensuring fair distribution of the burdens and benefits of research. Subjects should be selected for participation for reasons directly related to the questions under study.
- Subjects must not be induced to participate in research projects by means or under circumstances that may overcome the voluntary nature of their participation. Enrollment into a study may never be the product of coercion or undue influence.

Investigator Qualifications and Responsibilities

- Research must be performed or closely supervised by individuals qualified by training and/or experience to minimize risks and otherwise protect subjects.
- Primary responsibility for research with human subjects is vested in the principal investigator conducting a study. This includes responsibility to comply with the laws, regulations, and institutional policies that regulate research. Others engaged in the conduct of the research such as co-investigators and research staff share this responsibility. The PI must assure that all study team members are appropriately trained to the protocol or study procedures.
- Investigators must follow HRPP Handbook for initial submission and approval of proposals, continuing review, amendment to the study, and reporting of unanticipated problems and adverse events. Investigators are responsible for informing IRBs of existing knowledge of any risks involved in participating in a study at the time of initial review and

for apprising IRBs of any new risks identified during the study.

- Investigators must explain to subjects, prior to their participation in research projects, the objectives of the research, the procedures to be followed, the risks and potential benefits of participation, and alternatives to participation, funding sources and conflicts of interest, where applicable. Individuals may participate as a subject only after voluntarily consenting to participation and must be made aware of their right to withdraw without risking benefits or services to which they otherwise would be entitled. In addition, in most cases, investigators will obtain the assent of subjects, such as minors or mentally incapacitated individuals, before participation. Investigators are responsible for ascertaining that subjects consenting or assenting to research comprehend the information provided to them before enrolling them in studies and that subjects are aware of their right to ask questions about the research before, during and after participation. IRBs may waive some of these consent requirements.
- Investigators must respect the privacy of subjects participating in their protocols and implement safeguards to protect the confidentiality of data gathered for the research.

Geisinger Institutional Review Board (GIRB)

- GIRB is authorized to review and to approve, approve with modifications, or disapprove any research involving human subjects in accord with their own standard operating procedures and applicable institutional policies.
- No human research may be conducted without IRB approval or notification of exemption.
- GIRB has the authority to suspend a study or terminate approval of a previously approved study.
- Board membership will meet applicable regulatory standards. Members will appropriately represent the varying perspectives of subjects, investigators, and the community at large. GIRB will solicit advice from external consultants as needed to ensure appropriate expertise on the boards and represent the views of particular subject populations. GIRB members will not participate in the approval of projects in which they are involved or otherwise have a conflicting interest.

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 or country 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 on the ethical principles governing human subjects research and investigator responsibilities are 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 in the standard contract templates a provision that the

sponsor acknowledges and understands that the Geisinger HRPP is applicable to all human participant research. (See Section 16- HRPP Coverage of Sponsored Research)

Legal Principles

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

- Federal Regulations (Common Rule) 45 CFR 46
- Food and Drug Administration Regulations 21 CFR 11, 50, 56, 312, and812
- 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) deviceresearch, where the IRB serves, in a sense, as the FDA's surrogate with respect to reviewand approval of NSR studies.
- Geisinger's Scientific Review Committee (SRC) provides a peer review of investigator- initiated protocols involving more than minimal risk that have not reviewed by the above-mentioned entities. The review primarily focuses on the scientific merit of the study and applies to all phases of clinical therapeutic intervention, behavioralclinical trials, tissue and body fluid research, and diagnostic trials that impact medical decision making for the treatment of patients. The process is described in the SRC website. The research team is provided a letter from the SRC documenting that the protocol was found to be meritorious. A copy of the letter must be included with the 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 federal research regulations [45 CFR 46.111(a) and 21 CFR 56.111(a)], whether the following requirements are satisfied:

a. 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.
b. 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, inputfrom hoc consultants may also be obtained. For further information, refer to Guidance Evaluating Sound Study Design.

Ethics Review

The IRB review of the study procedures, risks and benefits includes the identification, evaluation and resolution of the ethics issues presented in the study in accordance with the ethical principles outlined in Section 1.4. If necessary, the IRB may seek ad hoc assistance from the Chief Bioethics Officer and Assistant Professor of Geisinger Center for Translational Bioethics and Health Care Policy, who service as ex officio members of the IRB. In addition, Researchers and the IRB can get 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 the budgeting process, 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 Chief Scientific Officer (CSO)/Institutional Official (IO), pursuant to the authority delegated by the Chief Executive Officer (CEO) (see Delegation of Authority to Institutional Official). The CSO, through the Chief Administrative Officer, Research oversee 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 withadequate means to carry out its mission while keeping the protocols-to-staff-ratio within acceptable and manageable limits.

Resource Allocation in support of HRPP: The IRB receives its annual budget through the CSO.

During preparation of the annual budget the HRPP program is evaluated using statistics from the previous year's volume and complexity of studies to determine if resources are adequate to carry out an efficient and effective HRPP:

- IRB(s)
- Staffing
- Space
- Legal Counsel (an attorney is assigned for research support and questions)
- Community Outreach
- Funds for educational opportunities for IRB members and IRB staff,including off-site conferences
- Funds to provide on-going office and logistic support
- Funds to carry out agreed-upon special projects.

The annual budget is established by the following process:

1. The Director, IRB Operations and HRPP, Research Finance Offices, and CAO, Research prepare income and expense forecasts for the following year. Income forecast includes fees collected for the review of protocols on industry-sponsored clinical research.
2. The budget is reviewed and approved by the CEO and presented to the Board of Directors for approval. The budget takes effect on July 1 of each year.

During the fiscal year, the Director, IRB Operations and HRPP may analyze and explain any variance between actual income and expense (or projected income and expense) and the budget of the IRB, in accordance with the guidelines provided by the Finance/Budget Department. When unanticipated needs arise, they are communicated by the Director, IRB Operations and HRPP to the CAO, Research. These needs are considered in light of their urgency and fiscal implications.

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**)*

Geisinger IRB meetings are held twice a month – first and third Thursdays.

Geisinger 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 for the study is appropriate. A ceding acknowledgement letter is sent prior to submission of any studies to CIRB.

Geisinger participates in the Health Care Systems Research Network (HCSRN). A Reciprocal Reliance Agreement was signed with the participating sites to allow ceding of studies within the network. The Standard Operating Procedures outlines the policies and procedures for IRB review of research conducted in more than one member of the HCSRN.

Geisinger contracted with Western IRB (WIRB) for review of all multi-center industry and adult oncology clinical trials from 2006-2011. WIRB will retain the oversight of theindustry study clinical trials until study closure.

When Geisinger relies on the services of an external IRB such as NCI CIRB, HCSRN, or WIRB, Geisinger IRB confirms whether the ceded IRB has received AAHRPP accreditation. If so, no further evaluations are necessary to assure that the ceded IRB meets relevant accreditation standards. Any agreement (MOU, etc.) would detail how responsibilities are divided between Geisinger and the external IRB. This would include reporting non-compliance and unanticipated problems, conflict of interest, etc. and follow-up requirements necessary.

The IRB assesses activity at least annually to optimize the workflow and IRB load. 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 Chairs regarding the level of activity and other IRB- related matters are gathered in reports to the CSO. When adjustments are necessary, their financial implications are considered during the budget process outlined above in Section 2.1. New IRBs or new staff positions are created to meet the demands of theworkload.

2.3 iRIS by iMEDRIS

Geisinger's IRB utilizes an electronic submission process called iRIS. iRIS integrates Institutional Review Board (IRB) management and data collection all 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**)*

*The IRB 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**)*

To approve research, the IRB must determine that, where appropriate, there areadequate resources to ensure the care and safety of participants throughout the project, beginningwith 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 therequired number of participants; sufficient time to conduct and complete the research; adequate numbers of qualified staff; adequate facilities; a process to ensure that all personsassisting with the research are adequately informed about the protocol and research related dutiesand functions; and medical or psychological resources available that participants might require as a consequence of the research when applicable.

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

The IRB requires that appropriate communications from the following offices or committees are complete. The Pre-Review Checklist is used when reviewing a study submission to ensure that situations that require communication and interaction between various components of the HRPP are handled appropriately:

- **Radiation Safety Committee (RSC)** - The study team will forward a copy of the protocol to the RSC for review. The RSC must certify that it has reviewed a protocol using radioisotopes or radiation machines and recommends it for approval. A copy of the RSC approval must be uploaded with the submission to the IRB.
- **Institutional Biosafety Committee (IBC)** reviews protocols *involving biosafety materials*. The IBC review and approval must be completed prior to submission of the protocol to the IRB. The IBC provides an approval letter and a copy is uploaded with the submission to the IRB. If an amendment/ modification or continuing review involves review by the IBC, the IRB will hold its approval until IBC approval is uploaded with the submission 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 as necessary. COI Smart is an electronic system 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, the development of COI management plans, and data mining tools for auditing, tracking and reporting on potential conflicts of interest. The IRB will not approve a protocol until any disclosed COI has been reviewed and resolved by the Research Conflictof Interest Committee, and as appropriate, a plan or strategy toadequately eliminate, mitigate, or manage the conflict has been determined by the Research Conflict of Interest Committee (RCOIC). See Sections 3.7 - Conflicts of Interest (COI) and 6.6 - IRB Member, IRB Staff, and Consultant Conflicting Interest.
- **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 (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.

- **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 evidence-based nursing practice and nurse-initiated research. Any protocol involving nursing practice and/or nurse-initiated must have, as a condition of approval, a NRC Number from the NRC. The study application must include the NRC Number to identify that the NRC was contacted and reviewed the submission.
- **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 GIRB 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.
- **Corporate Communications -** The Corporate Communications department plays a crucial role in communicating the mission, vision and values of Geisinger to physicians, professional staff, volunteers, patients and the community at large. All Geisinger branded pamphlets and posters, etc., for subject recruitment must be reviewed by Corporate Communications and documentation of the review uploaded with the study submission documents.

Interaction

The IRB coordinates interaction among key individuals who are responsible for human research participant protection.

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.

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 Element I.1.D)

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

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

The IRB maintains internal and external Human Research Protection Program websites which provide access to:

- The HRPP Handbook
- Links to pertinent governmental regulations and guidelines
- Links to relevant Geisinger policies (HRPP Handbook, and system policies)
- Guidance on various topics, such as sponsor-investigator research, childrenin research, use of test articles and reportable events
- ICH-GCP and HHS/PHS
- Checklists, consent/assent forms, and HIPAA authorization templates
- iRIS overview and instructions, help documents, and information
- Guidance for investigators regarding human subjects research protections and the IRB review process
- Research Determination Worksheet (RDW) information and forms to assist investigators in identifying which protocols involve human subjects research requiring IRB review.
- Alerts highlighting the posting of new information or changes in existing policies and procedures
- Educational/informative training presentations

The IRB utilizes the following mechanisms for communicating changes in policies, procedures, handbook, etc.

- Research News
- HRPP website updates, showing new effective dates
- Important iRIS Announcements – via a blast within the iRIS electronic IRB system

notifications, which are sent to all iRIS Users, including, Administrators, Investigators, Research Staff, IRB Members and Staff, Office of Sponsored Projects, Research Finance, Research Compliance, etc.

The IRB staff is readily available to assist investigators and research staff on human subjects research matters, particularly the study application and reviewquestions.

IRB member and staff education is provided at throughout the yearvia multiple mechanisms (i.e. educational retreats, presentations, etc.) Presentations are available to all IRB members.

The IRB staff regularly present training, often to large research groups, and accept invitations to attend classes and departmental meetings to provide information and guidance to the Geisinger research community on IRB policies and procedures governing human subjects research.

Within the IRB, dedicated staff are responsible for identifying new informationimpacting human research participant protection such as new organizational policies, or emerging ethical and scientific issues. Information about new or modified laws and regulations might also be identified by others within the research community, including Geisinger Center for Translational Bioethics and Health Care Policy and Department of Legal Services. New information is posted on the HRPP website and is disseminated to the IRB staff, IRB members and the Geisinger research community.

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 Chief Scientific Officer (CSO)/Institutional Official (IO) as specified in the Delegation of Authority letter.

The CSO officially appoints the IRB chairs. The Director, IRB Operations and HRPP, after consultation with the IRB chairs, appoints the IRB members. The CSO assigns theauthority and responsibility of the chairs 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 covered organizations, if needed, to ensure protection of human research participants. The IRB authority, membership requirements, and responsibilities are described in Section 6.

Delegation to the IRB

The CSO delegates independence and authority to the IRB through this Section and the Charge to each IRB Chair and/or Co-Chairs and IRB members at the time of appointment. The IRBs have 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
- Observe, or have a third party observe the conduct of research

Prohibition against Others Usurping IRB Approval Authority or Using Undue Influence

The CSO 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 will be reviewed by the CSO in the same manner as possible non-compliance by an IRB Chair or IRB member as described in Section 3.9. Attempts to unduly influence IRB members or staff are reviewed as appropriate to the situation, by either the Director, IRB Operations and HRPP or CSO.

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. (**AAHRPP Element I.1.A**)*

Human subject research is defined under 45 CFR 46.102, 21 CFR 50.3

The IRB retains ultimate authority to determine whether an activity meets the definitionof human subject research. IRB staff will make a timely determination after receipt and review of a completed Research Determination Worksheet. Outcome of the IRB staff review is communicated to the PI via correspondence. The correspondence provides documentation on whether the activity meets the definition of human subject research as defined in the HRPP Handbook.

Section 1.4 describes the types of human subjects research conducted at Geisinger.

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

Pilot Studies

A pilot study is defined as a preliminary investigation of the feasibility of a study, usuallydone on a small scale (e.g., fewer than 10 subjects) and exploratory in nature. It is designed to help the investigator refine data collection procedures and instruments or prepare a better, more precise research design, e.g., "how could this survey question be misunderstood?" See Guidance - Use of Human Subjects in Pilot Studies, Oral Histories and QA/QIProjects

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 the following federal regulations and Geisinger HRPP Guidance:

- **Federally sponsored research** - HHS Final Rule (2018 Revised Common Rule), 45 CFR 46.104. Please note: Geisinger is not making exempt determinations based on 2018 requirements for Exemption categories 7 and 8.

- F**DA-regulated research** - 21 CFR 56.104, which includes *Emergency use of a test article. (See Section 5.7 - Other Access to Investigational Drugs and/or Devices)***Minimal risk research that is neither Federally sponsored or FDA-regulated** - The IRB evaluated all ongoing studies for transition to HHS Final Rule Exemption categories 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. All reviewed on or after January 21, 2019 will follow HHS Final Rule. Please note: Geisinger is not making exempt determinations based on 2018 requirements for Exemption categories 7 and 8.

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 (drugs or devices, etc.), except as allowed in 21 CFR 56.104

IRB staff refer to Geisinger IRB Reviewer Form and *Guidance - Exempt Review Categories* , to verify that the PI has requested an appropriate exemption under the appropriate category.

Confirmation of exempt status is made by IRB members or designated IRB staff that has the knowledge and authority to confirm exemption.

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 or FDA-regulated; effective January 21, 2019 for all research unless FDA-regulated*) Please note: Geisinger is not making exempt determinations based on 2018 requirements for Exemption categories 7 and 8:

- **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 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

Those 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 – *(see Section 6.6- IRB Member, IRB Staff, and Consultant Conflicting Interest*) for 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)*

The IRB ascertains that exempt protocols provide appropriate protection of privacy and confidentiality interests. *(See Section 11- Privacy and Confidentiality)*

Exempt Review Process

PIs are required to submit the iRIS Exempt Study Application. In reviewing the application, IRB staff shall refer to *Guidance - Exempt Review Categories* and IRB Reviewer form to verify:

- Whether the PI has requested an appropriate exemption, and
- That exemption, if granted, is assigned under the appropriate category.

The 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.

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. Study determinations are based on Exemption criteria are described in Guidance - Exemption Categories, *IRB Reviewer Worksheet* and *Exempt Study Application*. Any change to the study's determination will be communicated to the study PI in the Review Outcome Letter and documented in the study's electronic IRB record.

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 or FDA-regulated; effective January 21, 2019 for all research unless FDA-regulated*) Please note: Geisinger is not making exempt determinations based on 2018 requirements for Exemption categories 7 and 8:

- **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, a letter is generated and sent to the PI and designated study contact.

If a protocol does not meet criteria for exemption, an IRB outcome letter will be sent to the PI and study contact requesting modifications. The letter will include details specifying why the submission failed to meet the exemption criteria. As applicable, the PI will re-submit the protocol using a Study Application for expedite or convened review.

Once a protocol is determined to be exempt, it is not reviewed again unless a protocol amendment/modification includes modifications that no longer qualify as "exempt". There is no continuing review process for exempt research. If the federal support status of a study reviewed and granted an Exemption, it is the responsibility of the Principal Investigator to notify the IRB immediately via amendment/modification.

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)

The IRB requires that PIs 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 a conflict within the regulations/laws, the IRB follows the most stringent of the regulations to assure adequate compliance and human subject protection.

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 state's 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.**)*

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 test 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.

DEFINITIONS:

1. ***Financial Conflict of Interest***: A Financial Conflict of Interest exists when Geisinger, through the RCOI committee reasonably determines that an Investigator's Financial Interest is related to a Research project and could directly or significantly affect the design, conduct or reporting of the Research.
2. ***Financial Interest***: A Financial Interest includes anything of monetary value, whether or not the value is readily ascertainable. The term, Financial Interest, **does not** include the following:

    - Salary, royalties, or other Remuneration paid by Geisinger to Investigators employed or appointed by Geisinger, including:
        - Intellectual property rights assigned to Geisinger and agreements to share in royalties related to such rights;
        - Income from investment vehicles, such as mutual funds and retirement accounts, as long as the Investigator does not directly control the investment decisions made in these vehicles;
        - Income from seminars, lectures, or teaching engagements sponsored by a federal, state, or local government agency, an Institution of higher education as defined at 20 U.S.C. 1001(a), an academic teaching hospital, a medical center, or a not-for-profit Research institute; or
        - Income from service on advisory committees or review panels for an Institution of higher education as defined at 20 U.S.C. 1001(a), an academic teaching hospital, a medical center, or a not-for-profit Research institute.

3. ***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 as a result 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 all non-research related conflicts of interest.

4. ***Institutional Financial Interests***: means the following financial or business interests of Geisinger:

- Royalty arrangements: payments, including royalty payments and licensing fees, resulting from technology transfer, licensing, and business activities;
- Non-publicly traded equity: equity and ownership interests of any amount in any for-profit entity that is not publicly traded;
- Publicly-traded equity: equity and ownership interests in the preceding twelve (12) month period in any publicly-traded, for-profit entity, except for equity held in Geisinger's endowment; and
- Gifts from any for-profit entity or philanthropic unit associated with a for-profit entity.

5. ***Research Conflict of Interest Committee (RCOIC):*** A committee established by Geisinger to review research conflict of interest disclosures from all investigators to determine if a potential conflict of interest exists in current research studies. The RCOIC considers the conflicting interests, determines or assesses any mitigation or management plan, and determines whether the conflict can be managed or needs to be eliminated. If further review is appropriate, the case is examined by the Chair of the RCOI and consultation with Chief Scientific Officer (CSO) if necessary. A Chair of the IRB and Director, IRB Operations and HRPP are also members of the RCOIC.

6. ***Research Conflict of Interest Committee Chair***: The RCOIC Chair is a member of the RCOIC and is responsible for overseeing the implementation and enforcement of Research Conflict of Interest Policy. The RCOIC Chair reports decisions to the Chief Scientific Officer (CSO) and ICOIC as necessary.

7. ***Intellectual Property Management Committee:*** A committee appointed to review, discuss, and evaluate new ideas, business relationships, partnerships, collaborations, etc. If any potential institutional conflicts of interest are identified, the Chief Administrative Officer for Research facilitates review by the Institutional and Research Conflict of Interest Committees. If the ICOIC or RICOC determines that an institutional conflict of interest may exist, the conflict of interest must be managed and minimized or eliminated.

Policies for Research

Geisinger Policy 14.702 on Financial Conflicts of Interest in Research, outlines the policy regarding conflict of interest (COI) for research conducted by Geisinger investigators. Each investigator must report to Geisinger all his/her financial interests at least annually using Geisinger's Annual Conflict of Interest Questionnaire. Geisinger reserves the right to request additional information and supporting documentation as needed. Non-Geisinger investigators named on Geisinger protocols must comply with their institutional FCOI policies if such policies follow federal financial conflict of interest regulations (42 CFR 50.601). If not, the external investigators must comply with Geisinger FCOI Policy 14.702.

Each investigator must update his/her Annual Conflict of Interest Questionnaire within thirty (30) days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new Financial Interest or any information previously reported to reflect any changed circumstances.

In addition, requirements related to potential conflicts of interest of the institution, its employees and leaders are addressed in Geisinger Legal Services policies:

- 09.100 – Conflicts of Interest Policy for Employees and Institutional Conflict
- 09.200 – Conflicts of Interest Policy for Directors and Officers

Role of the IRB

The IRB has the final authority to decide whether the potential conflict of interest and its management, if any, allows the research to be approved.

- When there are non-substantive outstanding COI matters, a protocol may be approved contingent upon the matters being resolved (e.g., requiring that the investigator modify the informed consent document to include verbatim language).
- When there are substantive outstanding COI matters, a protocol will either be tabled or disapproved until matters are resolved.

When a potential conflict of interest has been identified by the investigator on the Conflict of Interest Attestation portion of the study application, IRB staff consult with ORC staff regarding a management plan. When appropriate, a plan or strategy to adequately eliminate, mitigate, or manage the conflict must be determined by the RCOIC, reviewed and approved by the convened IRB. *(See Section 14.1- Detection of Harm, Minimization of Risks and Mitigation of Potential Injuries)*

When a known potential conflict of interest is discovered after the IRB review and approval of a study, staff will ask the PI to update the conflict of interest disclosure in COI Smart. The IRB will assess whether any action should be taken in accordance with Non- Compliance with HRPP Requirements in Section 3.8.

If the RCOIC determines that an institutional COI exists, the IRB staff will flag the iRIS sponsor database with a notation (Contact-Research Compliance). Each future submission with the flagged sponsor will be routed to ORC staff to verify that no conflict of interest exists. If conflicts are identified, a management or mitigation plan must be provided to the IRB for review with the submission.

3.8 Non-Compliance with HRPP Requirements

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 has and follows written policies and procedures for addressing allegations and findings of non-compliance with Human Research Protection Program requirements, and works with the Institutional Review Board, when appropriate, to ensure that participants are protected when non-compliance occurs. Such policies and procedures include reporting these actions, when appropriate. (AAHRPP Element I.5.D)

Geisinger requires researchers (investigators and others employed by, on staff at, or otherwise affiliated with Geisinger) to comply with all applicable local, state, and federal laws and regulations in the conduct of human research studies. As part of this requirement, researchers are required to submit written reports of events that meet the definition of "research non- compliance".

Any perceived or actual, serious or continuing non-compliance jeopardizes Geisinger's commitment to human subjects research protection. Mechanisms for identifying potential or

actual non-compliance are essential for accountability and education purposes, as well as correcting non-compliance, eliminating or reducing the possibility of re-occurrence, and attempting to mitigate any adverse effects on research participants.

Federal regulations 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)(2) require Geisinger to have written procedures which the IRB will follow for ensuring prompt reporting to the IRB, Office of Research Compliance (ORC), appropriate institutional officials, and when applicable, the Food and Drug Administration (FDA), and Office of Human Research Protection (OHRP) any serious or continuing non-compliance with the regulations or the requirements or determinations of the IRB.

See Guidance - Prompt Event Reporting to the IRB for guidance on prompt reporting.

Non-compliance: Failure to comply with federal regulations, state laws, Geisinger policies or procedure, and/or the policies, requirements or determinations of the Institutional Review Board (IRB), or provisions of the IRB-approved research study. Non-compliance with IRB and/or federal requirements may involve a range of issues from relatively minor or technical violations which result from inadvertent errors, inattention to detail, or inadequate training and supervision of research staff to more serious violations which pose risk to subjects and/or violations of their rights and welfare. This may pertain to the PI, research staff, or any member or component of the human research protection program.

Examples:

- Performing human subject research without first obtaining IRB approval or an IRB exemption determination.
- Failing to secure IRB approval of a protocol due for periodic continuing review prior to its expiration date.
- Inadequate supervision of the study and study staff by the PI
- Enrollment of subjects after IRB-approval of study expired or lapsed;
- Failure to obtain informed consent, i.e., there is no documentation of informed consent, or informed consent is obtained after initiation of study procedures;
- Performing study procedure not approved by the IRB;
- Failure to report serious unanticipated problems/adverse events involving risks to subjects to the IRB and (if applicable), the sponsor – See Guidance Unanticipated Problems vs Adverse Events;
- Failure to follow safety monitoring plan.

Continuing non-compliance: A pattern of repeated actions, instances or omissions by an investigator or study team member. Repetition may be the same instance or repetition of different instances. The repetition may be in the same or in different protocols by a single investigator and the likelihood that non- compliance will continue without intervention. A pattern of non-compliance that indicates lack of attention to or knowledge or understanding about regulations or ethics may affect the rights and welfare of participants. This behavior could compromise the scientific integrity of the study such that important conclusions could no longer be reached. The repetition may be in the same or in different protocols by a single

investigator and the likelihood that non- compliance will continue without intervention. Such patterns of behavior may indicate a deficiency in the ability or willingness to comply with Federal, State, and local regulations, Geisinger policies or the determinations and requirements of the IRB relating to human subjects research.

Examples:

- Frequent instances of minor non-compliance.
- Failure to respond to a request to resolve an episode of non-compliance.

Serious non-compliance: An incident of non-compliance that may compromise the rights and welfare of a subject or compromise the integrity of the research or study data. A single instance of non-compliance may be determined by the IRB to be serious non-compliance.

Examples:

- Failure to obtain prospective IRB approval of the research.
- Failure to obtain informed consent of subject(s).
- Enrollment of subject(s) who do not meet all eligibility criteria without prior approval from the sponsor and notification to the IRB.
- Enrollment of subject(s) while the study approval has lapsed.
- Inadequate supervision in research involving experimental drugs, devices or procedures.
- Failure to follow recommendations made by the IRB to ensure the safety of subjects.
- Failure to perform follow-up as outlined in the protocol, where the lack of follow-up potentially places the subject at increased risk of harm.
- Failure to report a serious unanticipated problem involving risks to subjects or others, including adverse events

Allegations of research non-compliance can be made through multiple mechanisms and the IRB bears the responsibility for initiating the investigation on all such reports. Formal reports must be within the iRIS electronic IRB system via submission of a Prompt Report Form within 5 working days of discovering the possible incident of non-compliance.

Minor or administrative protocol violations do not "**affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects**." Minor protocol violation must be reported to the IRB with the continuing review or final report submission. The Event Report Summary Sheet is an example of a form that can be used. See Guidance –Prompt Event Reporting to the IRB and Guidance – Unanticipated Problems vs. Adverse Events.

Once the report is received, the IRB staff conduct a preliminary review to verify whether appropriate details are included. If appropriate details areincluded in the report, the IRB staff completes an initial fact gathering process and make one of the following recommendations:

1. Allegation of research non-compliance not determined/unfounded
2. Minor research non-compliance/protocol deviation
3. Further review of possible research non-compliance by the IRB
4. Further review of possible research non-compliance by the Research Investigative Committee (RIC)

The goal for the IRB in investigating and managing issues of potential non-compliance, include:

1. Assuring the safety of human participants;
2. Developing action plans to prevent recurrence, and promote future compliance;
3. Educating research staff to ensure the understanding of FDA and OHRP guidelines and regulations, and Geisinger IRB Policy;
4. Reporting serious or continuing non-compliance, as appropriate.

Allegation of research non-compliance not determined/unfounded

If preliminary review by the IRB staff determines that an incident of research non-compliance did not occur, the investigator(s) will be notified in writing. The affected investigator(s) will be notified in writing within 30 working days of the final determination by the IRB. See Guidance – Prompt Event Reporting to the IRB.

Minor research noncompliance/ protocol deviation

If the preliminary review by the IRB staff determines that the incident is a minor research non-compliance or deviation from outlined protocol, the affected investigator(s) will be notified in writing within 30 working days of the final determination by the IRB and instructed to include the event at time of Continuing Review. See Guidance – Prompt Event Reporting to the IRB.

Review of research noncompliance

Referral to Research Investigative Committee (RIC)

If the preliminary review by the IRB staff determines that the incident is more than minor research non-compliance and involves multiple areas of the institution, such as, HIPAA, Pharmacy, ISO, etc. the IRB staff will forward to ORC for review. When appropriate, ORC will refer to the Research Investigative Committee (RIC) to ensure that the proper investigative channels are used according to appropriate expertise and jurisdiction and that the plan to address the reported improper research-related activity is appropriate to the circumstances; and that appropriate reporting occurs to the Institutional Official (IO), and others as necessary. The RIC review will include representation from the affected areas of the institution. If a RIC meeting is convened to review the incident, the Principal Investigator and coordinator/staff will be invited to attend the RIC meeting to discuss the incident and answer questions from the committee; they will leave the meeting for the committee discussion and/or deliberations. ORC staff will present findings to the RIC and provide additional information as requested. The RIC shall have available for its consideration the report of research noncompliance and any audit or other reports generated as part of the initial fact gathering process.

ORC and/or RIC will make recommendations for possible corrective action appropriate to the

noncompliance. Those recommendations will be forwarded to the IRB and any other appropriate involved parties or committees as appropriate. The IRB will begin the review process:

- The IRB staff will assign review to an IRB member reviewer(s) to determine whether the review can be completed via expedited or must be reviewed at a convened committee meeting based on the RIC risk assessment review.
- The IRB member reviewer(s) and/or convened IRB will review the RIC recommendations and relevant documents, including a summary of the allegation and the investigation.
- After review of non-compliance, the IRB's final determination shall be sent tothe affected investigator(s) with a copy to Institutional Official (IO) and others as necessary.
- The IRB staff will notify the ORC upon the completion of the corrective action plan by the Principal Investigator.
- ORC staff will provide periodic outcome reports to the Research Compliance Committee.

Referral to Privacy Office

Incidents of non-compliance, which include unauthorized disclosure of PHI are reported directly to Geisinger Privacy Office for review, investigation and recommendations regarding reporting and prevention of further disclosures.

Referral to Other Institutional Officials and/or Committees

At any point during the initial fact gathering process or later, when the IRB and/or ORC staff and/or RIC determines that the facts raise issues apart from or in addition to research non-compliance with applicable federal, state, and local laws and regulations or the requirements or determinations of Geisinger, the relevant aspects will be shared with other institutional officials for review or other remedial or correction action. The investigation of research non-compliance may occur in parallel with review under other institutional processes. Referral to such other processes may not affect any continuation of investigation or course of investigation.

IRB Review, Outcome, Recommendation(s), and Reporting

The convened IRB reviews to make a determination as to whether the event constitutes serious or continuing non-compliance. The outcome and recommendation of actions may vary depending on the severity of the non- compliance and the potential for continuing risk to participants. The range of actions could include items listed below, but the list does not preclude taking additional actions as determined on a case-by-case basis:

- Suspension of the study pending IRB receipt of further information from the PI in a period not to exceed 90 days;
- Modification of the protocol;
- Modification of the information disclosed during the consent process;
- Providing additional information to current participants (this must be done whenever the information may relate to the participant's willingness to continue

participation);

- Providing additional information to past participants;
- Requiring current participants to re-consent to participation;
- Alteration of the frequency of continuing review;
- Observation of the research or the consent process;
- Requiring additional training of the investigator and/or study team members;
- Notification of investigators at other sites;
- Obtaining additional information;
- Termination or suspension of the research. Such action will be reported to the IO.

All IRB determinations and actions are recorded and communicated, as appropriate, to the relevant involved individual(s), including the PI and study contact within 30 working days of final determination. IRB determinations of serious or continuing non-compliance are reported internally and externally as described in Section 3.10 – Internal and External Reporting.

HRPP Review of Research Non-Compliance Reports on Studies Ceded to an External IRB (WIRB, NCI CIRB, HCSRN, etc.)

All reports of allegations of research non-compliance in human subjects research where IRB review was ceded to an external IRB must include reporting to the IRB of record and follow with reporting to Geisinger IRB. The reports can be made through multiple mechanisms; however, the investigator must follow the reporting requirements of both the external IRB as well as Geisinger's HRPP requirements. The IRB of record and Geisinger ORC staff both have a responsibility to initiate investigations and follow-up on all such reports.

When Geisinger IRB staff receive a report of alleged non-compliance the report is assigned to ORC staff and are tracked electronically by both the IRB and ORC staff and reported periodically to the Research Compliance Committee. If appropriate details from the external IRB are included, the ORC staff completes a review and if necessary forwards to the RIC for recommendations and completes any necessary external and internal reporting requirements.

1. If the allegation of research non-compliance not determined/unfounded no further reporting or follow-up is necessary and an acknowledgement is sent to the PI.
2. If the allegation is determined to be a minor research non-compliance/protocol deviation a letter will be sent to the PI acknowledging ORC review.
3. If the allegation requires further review of possible research non-compliance the ORC staff conducts further investigation and sends correspondence requesting additional clarification.
4. If further review of possible research non-compliance requires review by the Research Investigative Committee (RIC), or other involved parties the PI will be notified and asked to attend the RIC meeting to provide information to the committee.

The ORC staff will formalize a final letter of outcome to the PI with copies to the appropriate internal and external parties, which could include the IO, sponsor, funding agency, etc.

Non-Compliance Involving an IRB Chair (s), IRB Member (s) or ORC and /or IRB Staff

The Chief Scientific Officer (CSO) is responsible for investigating and reviewingnon-compliance involving IRB Chair(s), IRB member(s), IRB staff, ORC staff, or the Director, IRB Operations and HRPP. If a fact-finding review of an allegation is necessary to assess the evidence, the CSO and his/her designee will investigate, conduct the appropriate review, and request additional assistance as needed.

Any disciplinary action necessary must follow the appropriate Geisinger Human Resources Policy.

DEFINITIONS:

Administrative Hold: An administrative hold is a voluntary action by an investigator to temporarily or permanently stop some or all approved research activities. Administrative holds are not suspensions or terminations. Protocols on administrative hold remain open and require continuing review as required by the IRB.

Allegation of non-compliance: An unproven assertion of non-compliance that must be proved or supported with evidence.

Continuing non-compliance: A pattern of repeated actions, instances or omissions taken by an investigator or study team member. Repetition may be the same instance or repetition of different instances. A pattern of non-compliance that indicates lack of attention to or knowledge or understanding about regulations or ethics may affect the rights and welfare of participants. This behavior could compromise the scientific integrity of the study such that important conclusions could no longer be reached. The repetition may be in the same or in different protocols by a single investigator. There is a likelihood that non-compliance will continue without intervention. Such patterns of behavior may indicate a deficiency in the ability or willingness to comply with federal, state, and local, and institutional regulations, Geisinger policies or the determinations and requirements of the IRB relating to Human Subjects Research.

Department of Health and Human Services (DHHS): The United Statesgovernment's agency for protecting the health of all Americans and providing essential human services, especially for those who are least able to help themselves.

Directed Audit: Audits conducted by the ORC staff designed to assess the investigator's compliance with federal regulations, state and local laws, and IRB policies and procedures. These audits of IRB approved research studies are in response to identified concern(s). Concerns may be identified by an IRB Committee, an external source (e.g. OHRP, FDA or Sponsor), or an internal source (e.g. participant, family member, or Institutional personnel). Audit reports are provided to the requesting part, IRB, Compliance Committee, and CSO asrequired.

Finding of non-compliance: Non-compliance has been determined to be true, or anallegation of non-compliance that is determined to be true, based on a preponderance of the evidence.

Food and Drug Administration: The federal office responsible for implementing regulations governing the use of investigational drugs, biologics, devices and radiological procedures including radioactive drugs in clinical investigations with humans.

Generalizable Knowledge: The HRPP defines this as information that is gathered by a research protocol or project that answers a research question (i.e., hypothesis). Resultant information should be able to be applied to the general population relative to the population targeted.

Greater than Minimal Risk: Where the research involves greater than minimal risk (defined below) to subjects, the mechanism of obtaining local research context differs depending on whether the local research context involves intervention or interaction with subjects and whether the principal risk associated with the local research context is limited to the potential harm resulting from a breach of confidentiality.

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

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

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

a. **Intervention:** Includes both physical procedures by which data are gathered (e.g., venipuncture) and manipulations of the subjects' environment that are performed for research purposes.

b. **Interaction**: Includes communication or interpersonal contact with a subject or their private identifiable information.

c. **Private Information**: Includes information about behavior that occurs in a setting in which an individual can reasonably expect that no observation or recording is taking place. It includes information, which has been provided for specific purposes by an individual, and the individual can reasonably expect will not be made public (e.g., a medical record). Private information must be individually identifiable to be considered information to constitute research involving human subjects. This may include identifiable private information obtained from a primary subject about a third party.

Human Subjects Research: Any research that involves humans as subjects.

Minimal Risk: 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.

Minor (Administrative) Non-Compliance: Any non-compliance that is not serious or continuing non-compliance and that does not affect the rights and welfare of participants or put participants at risk of harm.

Non-compliance: Failure to comply with federal regulations, state laws, Geisinger policies or procedures, and/or the policies, requirements or determinations of the Institutional Review Board (IRB), or provisions of the IRB-approved research study. Non-compliance with IRB and/or federal requirements may involve a range of issues from relatively minor or technical violations which result from inadvertent errors, inattention to detail, or inadequate training and supervision of research staff to more serious violations which pose risk to subjects and/or violations of their rights and welfare. This may pertain to the PI, research staff, or any member or component of the human research protection program.

Office for Human Research Protections (OHRP): The office under the Departmentof Health and Human Services responsible for implementing DHHS regulations (45 CFR 46) governing biomedical and behavioral/social science research involving human subjects.

Periodic Compliance Review: Random assessments of the internal HRPP department and external departments or sites involved in the conduct of human subjects research at Geisinger conducted by ORC staff. These reviews are used to evaluate proper execution and accurate

documentation of an IRB approved research project. Internal compliance reviews monitor the adherence to federal regulations, state and local law, and IRB policies and procedures as well as accurate documentation in the IRB database. External compliance reviews monitor the adherence to federal regulations, state and local law, Geisinger IRB policies and procedures, adherenceto the study protocol, accurate documentation and reporting of study related activities, and evaluation/observation of the informed consent process.

Quality Improvement/Auditing: A methodology employed by the IRB staff, when needed, to improve existing processes by identifying the root cause of a problem, developing and implementing an action plan, and evaluating the outcome to assure problem resolution. Reports will be forwarded to the required parties, compliance committee, and IO as necessary.

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

Research Investigative Committee (RIC): A committee that includes the Manager of ORC, staff of the Office of General Counsel,and other departments, such as, Internal Audits, HIPAA Privacy Office, IRB, and/or Institutional Official and additional members as the need arises. The Manager of the ORC will chair the Committee meetings and proceedings and maintain a master file of all committee proceedings. The Research Investigative Committee will serve to ensure coordination and review of investigations.

Serious non-compliance: Failure by investigator or study personnel to comply with laws or regulations, Geisinger policies, or determinations of the IRB when that failure may: 1) adversely affect the rights and welfare of human subjects; or 2) compromise the integrity of the research. A single instance of non-compliance may be determined by the IRB to be serious non-compliance.

Sponsor-Imposed Suspension: A determination from the sponsor of the study to place specific research activities on hold. This determination may be made for interim data analysis; inadequate drug availability; response to a DSMB report/recommendation; or a preplanned stopping point.

Suspension: A suspension of IRB approval is a directive of the convened IRB, or IRB designee either to stop temporarily some or all previously approved research activities, or to stop permanently some or all previously approved research activities. Suspended protocols remain open and require continuing review.
Termination: A termination of IRB approval is a directive of the convened IRB or IRB designee to stop permanently all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review.
Unfounded Report of Possible Incident of Non-Compliance: Review of report and facts does not support a finding of non-compliance, the report of the Possible Incident of Non-Compliance will be dismissed and no further action will be taken. The report of findings of fact and determinations will be sent to the Principal Investigator and, when relevant, any other affected investigator(s).

3.9 Unanticipated Problems Involving Risks to Participants or Others, and Other Reportable Information

*The IRB has and follows written policies and procedures for addressing unanticipated problems involving risks to participants or others, and for reporting these actions, when appropriate. (**AAHRPP Element II.2.F**)*

Geisinger researchers must comply with all applicable local, state, and federal laws and regulations in the conduct of human subject research. Researchers must submit to the IRB written reports of events that meet the definition of "unanticipated problems involving risks to participants or other." Problems or events labeled as "adverse events" in research involving investigational drugs or devices may or may not meet the definition of an unanticipated problem. The PI will make a preliminary determination whether the event meets the criteria of reportable. (See Guidance - Prompt Event Reporting to the IRB and Guidance – Unanticipated Problems vs Adverse Events)

Federal Regulations 21CFR56.108(b)(1) and 45CFR 46.108(i) require the IRB to "follow written procedures for ensuring prompt reporting to the IRB…any unanticipated problems involving risk to human subjects or others." FDA guidance documents recognize that:

1. "individual adverse event reports generally require an evaluation of their relevance and significance to the study, including an evaluation of other adverse events, before they can be considered to be an unanticipated problem," and
2. "All reports to the IRB of unanticipated problems should explain clearly why the event described represents a 'problem' for the study and why it is 'unanticipated."

Investigators must follow details outlined in the IRB approved protocol. If the principal investigator (PI) recognizes that an unanticipated problem (UP) or event has occurred special considerations for prompt reporting of the UPs or events must occur. This may occur because of an event that occurred at a Geisinger site or new information received by the investigator. Information about an event that occurred at another research site must be assessed by the PI to determine if it meets criteria for prompt reporting and then prompt reporting as required.

1. Event (including on-site and off-site adverse event reports, injuries, side effects, breaches of

confidentiality, or other problems) – that occurs any time during or after the research study, which in the opinion of the Principal Investigator (PI):

a. Involved harm to one or more participants or others, or placed one or more participants or others at increased risk of harm;
b. Is unexpected (an event is "unexpected" when it is not described with specificity in the protocol and informed consent document; or if described with specificity, it occurs beyond the expected frequency and/or severity identified); and
c. Is related to the research procedures (an event is "related to the research procedures" if, in the opinion of the principal investigator, it was more likely than not to be caused by the investigational product or research procedures).

2. Information that indicates a change to the risk to benefit ratio of the research. For example:
   a. An interim analysis indicates that participants have a lower rate of response to treatment than initially expected;
   b. Safety monitoring indicates that a side effect is more severe, or more frequent than initially expected; or a paper is published from another study that shows that an arm of the research study is of no therapeutic value.
3. Change(s) in FDA labeling or withdrawal from marketing of a "test article" (a drug, device, or biologic) used in a research protocol.
4. Change(s) to the protocol without prior IRB review to eliminate an apparent immediate hazard to a research participant.
5. Incarceration of a participant.
6. Event that requires prompt reporting to the sponsor.
7. Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
8. Protocol violation (a term often used by NIH or commercial sponsors, meaning an accidental or unintentional change to the IRB approved protocol) that placed one or more participants at increased risk, or has the potential to occur again.
9. An unanticipated adverse device effect as defined by FDA at 21 CFR Part 812.3(s).

How to Report

The PI must submit the Prompt Report Form in the iRIS electronic IRB system. Initial reports may be accepted by other means such as email or phone only if the report is of an urgent nature. The PI is still obligated to submit the Prompt Report Form in the iRIS electronic IRB system as soon as possible after the PI learns of the event but in all cases within 5 working days.

Minor or administrative protocol deviations that do not "affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects" do not require prompt reporting to the IRB and must be reported to the IRB when submitting the Continuing Review Report Form or Final Report Form. See Guidance. – Prompt Event Reporting to the IRB and Guidance – Unanticipated Problems vs Adverse Events.

If the PI recognizes a new problem/event that involves risk to subjects or others and the information is not already in the consent/assent document, he/she submits an amendment /modification form with a revised consent/assent document and protocol if applicable.

IRB Review

All IRB members, including assigned reviewers, have access to review all Prompt Reports. Unanticipated problems submitted to the IRB via Prompt Report Forms are assessed by IRB staff to determine if it meets the definition of an unanticipated problem involving risks to participants or others. Review of a problem or event may require use of a consultant, or assistance to collect additional information before a determination is made. The IRB has a range of available actions if an event is deemed to be an unanticipated event or other reportable information. The actions may vary depending on the severity of the event and the potential for continuing risk toparticipants. The range of actions could include items listed below, but the list does not preclude taking additional actions as determined on a case-by-case basis:

- Suspension of the study pending IRB receipt of further information from the PI;
- Modification of the protocol;
- Modification of the information disclosed during the consent process;
- Providing additional information to current participants (this must be done whenever the information may relate to the participant's willingness to continue participation);
- Making arrangements for clinical care outside the research or additional follow-up for participants;
- Providing additional information to past participants;
- Requiring current participants to re-consent toparticipation;
- Alteration of the frequency of continuing review;
- Observation of the research or the consent process;
- Requiring additional training of the investigator and/or study team members;
- Notification of investigators at other sites;
- Obtaining additional information;
- Termination or suspension of the research. Such action will be reported to the sponsor or funding agency, and CSO as necessary.

The IRB reviews all reports submitted either via expedited or convened IRB review. If the study is federally funded (e.g., by the Department of Health and Human Services), or is regulated bythe Food and Drug Administration, additional IRB reporting requirements may be required.

The CSO will be informed when a determination has been made that a problem or event meets the definition of an unanticipated problem involving risks to participants or others. The CSOwill fulfill the requirements to report the action to federal departments or agencies as required by regulation.

Any action taken by the IRB is communicated to the PI and study contact. If the IRB action will affect participants in the protocol (e.g., requires withdrawal of participants), the IRB considers the impact on their health and safety. *(See Section 9.4, Suspension or Termination of IRB Approval)*

If a determination is made that a problem or event does not meet the definition of an unanticipated problem involving risks to participants or others, no further action needs to be taken. The IRB staff sends a letter to the PI explaining that the event did not meet the criteria for prompt reporting.

HRPP Review of Unanticipated Problems (UPs) Involving Risks to Participants and Others on Studies Ceded to an External IRB (WIRB, CIRB, HCSRN, etc.)

All reports of Unanticipated Problems (UPs) involving risks to subjects or others where IRB

review was ceded to an external IRB must include reporting to the IRB of record and follow with reporting to Geisinger IRB. The reports can be made through completing the Prompt Report Form in iRIS; however, the investigator must follow the reporting requirements of both the external IRB as well as Geisinger's IRB requirements. The IRB of record and Geisinger ORC staff both have a responsibility to initiate investigations and follow-up on all such reports.

When Geisinger IRB staff receive the Prompt Report Form, the report is provided to ORC staff. Both the IRB and ORC staff electronically track all reports for periodic reporting to the Research Compliance Committee. If necessary, the ORC staff forwards to the RIC for review and recommendation. The ORC staff work with IRB staff to complete any necessary external and internal reporting requirements.

1. If the report is found to not meet the appropriate reporting requirements and no additional follow-up or reporting was found necessary, an acknowledgement letter is sent to the PI.
2. If the report is determined to be a minor protocol deviation and no additional follow-up or reporting was found necessary, an acknowledgement letter will be sent to the PI.
3. If the report requires further review, the ORC staff conducts further investigation and sends correspondence requesting additional clarification or further review.
4. If further review of the report requires review by the Research Investigative Committee (RIC), or other involved parties, the PI will be notified and asked to attend the RIC meeting to provide information to the committee.

The ORC staff will formalize a final letter of outcome to the PI with copies to the appropriate internal and external parties, which could include the CSO, sponsor, funding agency, etc.

DEFINITIONS:

"*Unanticipated problems involving risks to participants or others*" is definedas:

1. The event is unexpected in terms of nature, severity, or frequency, given:
   a. The research procedures described in the protocol and informed consent document; and
   b. The characteristics of the subject population being studied; and
2. The information indicates that participants or others are at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

"*Adverse event*" is defined as any untoward or unfavorable medical occurrence in a human research subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (See Guidance – Unanticipated Problems vs. Adverse Events).

"*Prompt reporting*" is defined by Geisinger as reporting of unanticipated problems or events as soon as possible after the PI learns of the event, but in all cases within 5 working days.

"*Protocol deviation*" Geisinger defines a minor or administrative departure (see Guidance – Prompt Event Reporting to the IRB) from the protocol procedures approved by the IRB that was made by the PI without prior IRB approval.

3.10 Internal and External Reporting

*Geisinger has and follows written policies and procedures for addressing allegations and findings of non-compliance with Human Research Protection Program requirements, and works with the Institutional Review Board, when appropriate, to ensure that participants are protected when non-compliance occurs. Such policies and procedures include reporting these actions, when appropriate. (**AAHRPP Element I.5.D**)*

*The IRB has and follows written policies and procedures for addressing unanticipated problems involving risks to participants or others, and for reporting these actions, when appropriate. (**AAHRPP Element II.2.F**)*

*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 reports the following decisions to the CSO if the convened IRB suspends or terminates the approval of a protocol pursuant to *Section 9.4, Suspension or Termination of IRB Approval.*

- serious or continuing non-compliance has occurred as specified above under *Section 3.8*, *Non-compliance with HRPP Requirements* or
- unanticipated problem (UP) or some other reportable event has occurred asspecified in *Section 3.9, Unanticipated Problems Involving Risks to Participants or Others, and Other Reportable Information.*
- suspensions or terminations

After review by the CSO, additional reporting will follow the written procedures for reporting Unanticipated Problems, non-compliance, suspension and termination follow the OHRP and FDA regulations (45 CFR 46.108(i); 21 CFR 56.108(b)).

Reporting

The IRB staff will provide a written report of IRB findings, any applicable actions and relevant supporting documents as required to CSO within 10 working days from the outcome of the convened IRB.

Distribution

All reportable decisions are sent to the applicable reporting party within 30 working daysfrom the receipt of the reportable event by the convened IRB, which couldinclude:

- Federally-sponsored research - the relevant Department or Agency head, anyapplicable regulatory body, and OHRP (i.e., NCI, NIH, NHLBI, etc.);
- Research that is subject to the Food and Drug Administration (FDA) regulations regarding human subjects (any activity that involves an approved or unapproved drug or medical device except for activities that involve the use of an approved drug or medical device in the course of medical practices, and any activity in which data is reported to or held for inspection by FDA), the sponsor and theFDA;
- Non-federally-sponsored research not subject to FDA or federal regulations regarding human subjects need only be reported to the sponsor after review by the Geisinger's Research Investigative Committee (RIC) which could include;
  - The relevant privacy officer, if the report involves any unauthorized use, lossor

disclosure of HIPAA protected health information as described in *Section 11, Privacy and Confidentiality*.
- The relevant information security officer, if the report involves a violation of the HIPAA electronic security requirements for protected health information as described in *Section 11, Privacy and Confidentiality*.
- Any other individuals who the Institutional Official, the IRB Chair or Director, IRB Operations and HRPP choose to notify (e.g., Department Chairs, Division Chiefs, administrators, the Department of Legal Services, etc.).

For any federally sponsored research, the report will include:
- The name(s) of the relevant Geisinger site, division, and department conducting the research
- The title and number of the IRB protocol and of any federal proposal or award in which the Reportable Decision occurred
- The name of the site Principal Investigator (PI)
- The name of the Principal Investigator (PI) on any applicable federal award if different from the site PI
- A detailed description of the Reportable Decision
- The actions taken or planned to be taken to address the circumstance(s) leading to the Reportable Decision.

No report is necessary if federal agencies have already been made aware of the event through other mechanisms such as the investigator or sponsor.

For multicenter research projects, only the institution at which the participant(s) experienced an adverse event determined to be an unanticipated problem (or the institution at which any other type of unanticipated problem occurred) must report the event to the supporting agency head (or designee) and OHRP (45 CFR 46.108(i)).

3.11 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.

3.12 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 Element I.5.B**)*

Quality Improvement Monitoring

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

Reporting of Quality Improvement Monitoring Results

Results of quality improvement monitoring activities are documented and reported to the Director, IRB Operations and HRPP, Institutional Official and other units within Geisinger as appropriate. These results, supplemented by other review results when available, provide a quantitative and qualitative measurement of compliance with theHRPP.

IRB Performance Metrics

The Director Office of IRB 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.

3.13 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.)

There are a variety of mechanisms available for contacting relevant individuals to bring concerns and suggestions, including:

- Reporting possible non-compliance as described in HRPP, Section 3.8
- Reporting possible unanticipated problems as described in HRPP Section 3.9
- Research Newsletter – monthly updates
- IRB staff meetings
- Research staff can send suggestions through a link from the IRB website.
- Contact information on Geisinger.org HRPP webpage
- Making general comments and suggestions and expressing concerns about othermatters, issues or processes involving the HRPP, including IRB review and operations to any person in the HRPP / IRB Office or to the Chief Scientific Officer (CSO).
- Internal Auditing and Corporate Compliance provide safeguards to reporter privacy, such information can be submitted anonymously, if desired, through Corporate

Compliance Program and Hotline found on the Corporate Compliance website.

The Director, IRB Operations and HRPP reviews any concerns or complaints related to the IRB and HRPP Program, and IRB members and Chairs. The Director, IRB Operations and HRPP may consult with the Chief Scientific Officer (CSO) as needed for resolution.

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 works with Geisinger staff and departments, and other institutions, to offer 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 at training sessions and on the Human Subjects Research websites.

IRB staff develop, facilitate, and provide education for IRB members, IRB staff, and theresearch community regarding human research protections.

Training and EducationPlanning

The Director, IRB Operations and HRPP receives input from IRB Leadership Committee, IRB staff and members of the research community for input on necessary education and training needs. The training plan could also incorporate input received from IRB members, IRB staff and investigators, and from HRPP monitoring and evaluation activities. Trends in research at Geisinger are considered, and new federal, state or local regulations (or published guidance documents) are integrated. Compliance activities (e.g., internal and external audits) could provide input into education programs.

Evaluation of Qualifications

IRB staff

IRB staff qualifications are reviewed during the hiring process and annually or as needed to ensure a high level of commitment to the HRPP. IRB staff is required to seek Certified IRB Professional(CIP) Certification after meeting the following minimum testing requirements:

1. A bachelor's degree plus two years of relevant human research protection program (HRPP) experience, completed on or before the first day of the applicant's chosen testing period **or**
2. Three years of relevant HRPP experience, completed on or before the first day of the applicant's chosen testing period.

The CIP program is designed specifically for individuals administering or overseeing the daily operations of IRBs. Professionals from varied IRBs—institutional, independent, industry, as well as other organizations involved with biomedical, social science, behavioral, and educational research—may be eligible for the CIP credential.

IRB member or Alternate Member

IRB Member or Alternate Member qualifications are reviewed by the Director, IRB Operations and HRPP during the recruitment process, and IRB and alternate members are formally appointed by the IRB Chair(s). Throughout the year, IRB members, including IRB Chairs, provide feedback toensure 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 HRPP 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. Afterthe individual meeting has been conducted, the chair(s) send an e-mail confirmation to the Director, IRB Operations and HRPP. The documentation becomes part of the membership roster files maintained in the IRB Office.

Also, at the end of the fiscal year a formal evaluation is conducted according to individual divisions and department policies as part of the Human Resource Policy.

ORC staff

ORC staff qualifications are reviewed during the hiring process and annually or as needed. ORC staff is required to seek Certified Healthcare Research Compliance (CHRC) Certification after meeting the following minimum testing requirements:

- **Active Compliance Professional:** Has a minimum of one year of full-time work experience in healthcare compliance, with at least 50 percent of job duties dedicated to compliance.
- **Allied Compliance Professional:** Has at least 1,500 consecutive hours of work experience in a healthcare compliance related position (hours obtained must be within the last two years.

An individual Certified in Healthcare Research Compliance (CHRC) is someone with knowledge of relevant regulations and expertise in compliance processes sufficient to assist the healthcare industry in understanding and addressing legal obligations, and promote organizational integrity through the operation of effective compliance programs.

Contributing to the Improvement of Expertise

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

Opportunities for continuing education in human research protections are announced on aregular basis. IRB member and IRB staff attendance is encouraged at regulatory and professional meetings and conferences both locally and nationally, and for web broadcasts and seminars at Geisinger and in the greater community.

Before an IRB member can serve as a reviewer they mustcomplete all the necessary training. The

IRB also provides specific training tailored to the review of certain protocol types, e.g. protocols involving genetics, banking, etc. IRB members' expertise is considered when assigning primary reviewers *(see Section 7- Systematic Review).*

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 material, available online and in printed format, or offered as courses or workshops. This includes, among others:

- Geisinger's Human Research Protection Program's internal and external webpages, with links to the Geisinger's HRPP Handbook, instructional information, FAQs, educational material, document templates, forms, and guidance documents.
- Access to required training through the interactive online Collaborative Institutional Training Initiative (CITI) Course: The Protection of Human Research Subjects.
- Regular communications from the IRB and ORC in Research News
- The Research website
- The iRIS electronic protocol submission system, providing instructional text and explanation as part of the application
- iRIS training and training manuals
- The Human Subject Protection Program (HRPP) Handbook

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 Policy 14.707 Research Education and Training requires all investigators and research staff complete the following research training:

- Good Clinical Practice (GCP)
- Human Subjects Research (HSR)
- Responsible Conduct of Research (RCR)

Geisinger's HRPP has contracted with a group of collaborating professionals through the University of Miami – Collaborative Institutional Training Initiative (CITI) to manage and provide the necessary educational materials for investigators and study staff engaged in human subjects research.

All research study staff included on the study application, **except** Participating Cliniciansand Collaborators must complete Human Subjects Research, Responsible Conduct of Research and Good Clinical Practice Training. The completion of the training courses must be done every 3 years. Any study staff that have completed human research training at another institution must contact ORC Staff to review the curriculum and determine if training requirements are met.
Training courses for all users is recorded in iRIS by IRB staff. The course name and datecompleted is recorded under the User Profile.

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)

There are different human research regulations depending upon the type of research under review; suchas, the FDA and HHS. The FDA web page Comparison of FDA and HHS Human Subject Protection Regulations outlines differences between FDA regulations and HHS 45 CFR 46 regulations for the protection of human subjects.

Research with FDA-regulated test articles may commence only after the IRB has approved the protocol (this includes recruiting, obtaining consent, and screening participants for a specific study that is subject to the IND) and:

5.1.1 determines that the research will be conducted under an applicable Investigational New Drug Application (IND) or Investigational Device Exemption (IDE); or

5.1.2 determines that the proposed use of any investigational device satisfies the FDA criteria for non-significant risk devices; or

5.1.3 determines that satisfactory justification has been provided by the investigator as to why an IND or IDE is not required.

To allow the IRB to confirm that the test article has a valid IND or IDE number and assure thatthe research does not begin until a valid IND is in effect, one of the following must accompany the submission to the IRB: 1) a copy of the FDA letter approving the IND or IDE; 2) the IND or IDE number printed on the sponsor protocol; or 3) documentation from the sponsor.

Please note: Review and approval of the submission by the IRB may be delayed without inclusion of appropriate documentation from the FDA.

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 ina 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 Administrationunder 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 theact, 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 CFR56.102).

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 jurisdiction 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 ofthe test article or as a control. A subject may be either a healthy individual or a patient. (See 21 CFR 56.102)

Off-La bel: 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 "Off-Label" and Investigational Use of Marketed Drugs, Biologics and Medical Devices.

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 new drug application (IND) is synonymous with "Notice of Claimed Investigational Exemption for a New Drug." An investigational drug must have an IND before it can be shipped, unless one of the exemptions outlined in 21 CFR 312.2 is met.

The IND number is captured on study application for research on the use of a drug, unless that research is exempt from the IND regulations. The IND number must either match the number on the sponsor protocol with the same title as the proposed research, or be listed on communication from the sponsor specific to the proposed research, or on communication with the FDA.

When research involves the use of a drug other than the use of a marketed drug in the course of medical practice:

- The drug has an IND; **or**
- The protocol meets one of the **FDA exemptions** from the requirement to have an IND (21 CFR312.2(b)).
    - **Exemption 1**
        - The drug product is lawfully marketed in the United States, and all of 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 requirements for institutional review (21 CFR 50) and informed consent (21 CFR 56).
            - The investigation is conducted in compliance with the requirements of 21 CFR312.7 (Promotion of 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 the FDA guidance for FDA's current thinking on exemptions from IND regulations for oncology

combination protocols IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products.

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**)*

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

Clinical investigations of devices are subject to the Investigational Device Exemptions (IDE) regulations, 21 CFR 812.

Investigational devices may only be used after research studies and associated documentation have been approved by the Geisinger Institutional Review Board (IRB) and any other governing committees, excluding the exemption which permits emergency use of an investigational device on a one- time basis per institution without IRB review and approval (21CFR 56.104(c)).

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.

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 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 final 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 legally marketed in the US that is used or investigated in accordance with the indications in the FDA-approved labeling.
- A diagnostic device (that is, an in **vitro diagnostic device**) if sponsor complies with applicable labeling requirements in 21 CFR 809.10(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.

- 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 thattime.
- 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.

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 of 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 personalinformation.
- The study has been reviewed by an IRB in accordance with 21 CFR 56, except for theinformed 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 CFR812.2(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, in the course of comparative studies involving Bacillus anthracis detection devices, it would be inappropriate not to report positive results if they occur in the course of aninvestigation.

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 theIRB 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 studysubmission.

See:

- Significant Risk (SR) and Non-Significant Risk (NSR) Medical Device Studies
- Frequently Asked Questions Medical Devices [FDA],
- Significant Risk and Non-Significant Risk Medical Device Studies [FDA]

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. Oversightat Geisinger is handled by the Radiation Safety Committee (RSC). See Policy 14.107 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 fromthe 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. Acopy 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, and require an IND, 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 forreviewing 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. If so, during the IRB review and submission process the IRB confirms that the investigator understands his or her additional responsibilities as the sponsor of the research, including reporting requirements to the FDA.

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 withthe

Geisinger Investigational Pharmacy policies. *(See Section 5.6 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 proceduresin 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 acondition 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 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 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 DeviceStudies
- Sponsor-Investigator Research Requirements (when a Geisinger investigator is the sponsor ona non-significant risk device).

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. (**AAHRPP Element I.7.B**)*

Geisinger policy 11.609, 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 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).

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 presented by the FDA in the form of the Consolidated Guidance for Good Clinical Practice (GCP).

5.6 Other Access to Investigational Drugs and/or Devices

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

- Emergency Use: *See Section 5.7 - Other Access to Investigational Drugs and/or Devices*
- Compassionate Use (or Single Patient/Small Group Access)
- Treatment Use (Larger Group/More Widespread Use)
- Continued Access
- Humanitarian Use Devices (HUDs)
- Orphan Drugs

DEFINTIONS:

Expanded access: Use of investigational new drugs and approved drugs where availability islimited 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

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 5 working days ***after the use***. Expedited IRB approval is not permitted in emergency use. Investigators might wish to 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 inwhich 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.

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 generally 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 5 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:

- ☐ Emergence 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
  - Signed consent form/HIPAA authorization or documentation that Exception from Informed Consent Requirements were satisfied.

☐ **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 15 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 5 working days after the use.

- Devices with an IDE - IDE sponsor must report the use to FDA within 5 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 toassess 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 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 studydrug.

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 3 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 whichare 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). Prior IRB approval of a HUD is required 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 an 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 Parts 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
- Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff - Humanitarian Device Exemption (HDE) Regulation: Q & A

Planned Emergency Research

Planned Emergency Research: Planned research in life-threatening emergent situations where obtaining prospective informed consent has been waived.

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 or 45 CFR 46.101 (i), 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 the FDA information sheet, Exception from Informed Consent for Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble (FDA). 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

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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 CSO 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 CSO in turn has the authority delegated to him or her from the Geisinger Chief Executive Officer (CEO). On a day-to-day basis, the IRB reports to the Chief Administrative Officer.

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 reviewprocess. 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 orinstitutional 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 ofanother 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 CSO.

Decisions of the IRB

IRB approval is always necessary before a research project involving research participantsmay 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 afinal determination.

Appeal Process

If an investigator has concerns with respect to procedures or decisions of the IRB, he/sheis encouraged to discuss the concerns with the IRB Chair(s) and/or Director, IRB Operations and HRPP; however, nofurther action on the submission can be taken until the investigator puts his/her concern(s) inwriting 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, afact-finder 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 withinGeisinger

The IRB is supported by the Office of the Institutional Review Board and reports to the CSO through the CAO. The CSO is the institutional official responsible for assuring compliance with Geisinger policies and external regulations on the use of human research participants and is the head of the Geisinger IRB. The CSO receives periodic reports from CAOsummarizing the nature and volume of the IRB activities.

Responsibilitiesto Regulatory Agencies

The IRB must comply with the requirements of all relevant federal regulatory andcompliance 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 suchcommunication.

For FDA-regulated research, clinical investigators generally 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 FDA Form 1572 (for drug and biologic studies) or an investigator agreement for device studies.

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 5.5- 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-Chairs, members/alternate members, 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 Chief Scientific Officer (CSO)/Institutional Official (IO). This review ensures that individual IRB Chairs 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 and FDA regulations (45 CFR 46.107 and 21 CFR 56.107). Additionally, the IRB shall include at least five members, with varying backgrounds to promote complete and adequate review, a nonscientific IRB member, educated and with experience in unambiguously nonscientific areas. These individuals may not have meaningful scientific or medical training or experience. Health professionals, regardless of discipline, may not be considered nonscientists. An unaffiliated member who is not otherwise affiliated with Geisinger and who is not part of the immediate family of a person whois affiliated with Geisinger. At least one nonscientist IRB member must always be presentto have a quorum. (See discussion of quorum in *Section 6.8- IRB Roster and Quorum Requirements*).

Appointment of Members and Alternates, Length of Service, and Duties

IRB members and alternate members are nominated from a variety of sources, including previous IRB members or alternate members, division chiefs, department chairs, complianceadministrators, faculty, hospital pharmacy and nursing staff, research laboratories, and senior administrative IRB staff. Consideration is given to balancing race, gender, expertise, and cultural backgrounds. Members and alternate members with expertise from various clinical disciplines are sought as needed. 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 and international dimensions is valued. Annually, duringevaluation of members and alternate members, if gaps are identified an active search for new nominees is conducted. Identified nominees are contacted by the Director, IRB Operations and HRPP about their willingness to voluntarily serve on the IRB. When a nominee agrees to serve on the IRB, his or her Biosketch or CV and any relevant correspondence are reviewed by the Director Office of IRB and HRPP in collaboration with the IRB Chair(s) with input from the CSO.

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

(See Section 6.6- IRB Member, IRB Staff, and Consultant Conflicting Interest)

After a review of a potential member or alternate member's education, experience and other characteristics that might add diversity to the IRB, a new IRB member or alternate member receives a formal appointment letter from the IRB Chair(s). Members and alternate members serve an annual renewable term (generally from July 1 to June 30 but could vary dependingupon need). At the end of the fiscal year, members and alternate members' contributions are evaluated by the IRB Chairs with the Director, IRB Operations and HRPP *(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 members and alternate members may be re-appointed at the end of their term without lapse in service.

Members and alternate members 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.

Qualification to Perform Expedited Review

An IRB member or alternate member may perform protocol review according to the expedited procedure when the Director, IRB Operations and HRPP, in consultation with the IRB Staff and/or IRB Chairs, determines that the member or alternate member is "experienced" with regard to this purpose. There are several ways a member or alternate member may achieve sufficient experience, including attendance at IRB meetings, targeted education, working with a mentor or experienced reviewer, and previous IRB service. 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 asgeneral reviewers on all research. Members may also be asked to participate in continuing member education and training.

Appointment of IRB Chair, Length of Service, and Duties

IRB Chairs are nominated from a variety of sources, including previous and current IRB members or alternate members, division chairs, department directors, experienced researcher, etc. In addition to the characteristics sought in an IRB member or alternate member, these individuals possess demonstrated skills in leadership and group process. Chairs must have served on an IRB previously.

IRB Chairs are formally appointed by the Chief Scientific Officer (CSO)/Institutional Official (IO). Chairs serve a three-year renewable term (from July 1 to June 30). At the conclusion of the fiscal year (and interim, if needed) the IRB Chairs' contributions are evaluated by the Director, IRB Operations and HRPP with input from the CSO *(See Section 4- Knowledge of*

Human Research Protection Requirements). If their service is satisfactory, and their continued service is mutually desired, they are eligible forreappointment. The official appointment or reappointment letter is sent from the CSO.

In addition to the responsibilities of IRB membership, the Chair has primary responsibility for conducting IRB meetings and working with staff to ensure effective and efficient operation ofthe IRB within all applicable regulatory requirements. The IRB Chair works with IRB members, Director, IRB Operations and HRPP, institutional officials, and investigators to ensure that the rights and welfare of research participants are adequatelyprotected.

Compensation of IRBMembers

IRB Chairs' departments receive a percentage of their salary to offset the time dedicated to IRB duties. IRB members' and alternate members' departments also receive salary recovery tooffset the time dedicated to IRB duties. As the budget permits, IRB members and alternate members may also be eligible to receive a small award acknowledging their service on the IRB.

Since IRB members or alternate members who are not otherwise affiliated with Geisinger or its collaborating institutions are not able to receive salary recovery, a small annual honorarium is provided.

Alternate IRB Members

All IRB members (including alternates) are encouraged to attend all meetings. Alternate members are required to have the same qualifications and characteristics of expertise and diversity asthe regular IRB members for whom they substitute. All alternate members have access to allagenda material as regular members to allow them to substitute for a regular member.

The IRB membership rosters specify which regular member each alternate member is qualifiedto replace. The expertise or qualifications of alternate members are similar to those of the regular member they replace, and in some case, alternate members can represent similar interests or a specific vulnerable population. Terms of appointment, length of service, and duties areidentical to the regular IRB members. Alternate members must adhere to the same conflict ofinterest standards and documentation requirements as regular IRBmembers.

If an alternate member attends a convened meeting at which his or her regular member is in attendance, one of them does not vote.

Ex Officio IRBMembers

An ex officio member is designated as an IRB member by virtue of that individual's office. Some ex officio members serve on other Geisinger compliance committees and bioethics committee and may provide expertise to IRB members. Ex officio members may participate in the IRB deliberations to provide information and expertise as requested by the IRB. Ex officio members are expected to adhere to the same conflict of interest standards and documentation requirements as regular IRB members and alternates. Ex officio members may not vote on any IRB action or determination, and for this reason are sometimes referred to as "non-voting" members.

The IRB may accept additional permanent ex officio members with the agreement of theIRB Chair and the Director, IRB Operations and HRPP.

Liability Coverage for IRB members

Geisinger provides liability coverage under its insurance programs for IRB members acting ingood 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 a qualified staff, dedicated to supporting the IRB in its mission to protect human participants in research. The IRB staffing is reviewed at least annually by the Director, IRB Operations and HRPP, and Chief Administrative Officer per the current Human Resources policy to ensure they continue to provide sufficient resources to the IRB. The IRB staff has knowledge, skills and abilities appropriate to their respective roles. The Director, IRB Operations and HRPP oversees the IRB staff that represents the HRPP.

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 or scholarly expertise among IRB members allows the IRB to reviewthe broad variety of research in which Geisinger investigators are engaged. These policies and procedures require IRB members to be knowledgeable about all relevant regulatory requirements, and to strive to remain impartial and objective during protocol review, deliberation and voting. The IRB includes several members who are particularly knowledgeable about research ethics and the vulnerable research participants included in Geisinger research.

The IRB uses a "primary and secondary reviewer" system. The Director, IRB Operations and HRPP and/or IRB Specialist, in consultation with the IRB Chairs where appropriate, assigns protocols to primary and secondary reviewers, based on each individual's scientific, scholarly, professional, orclinical 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 Specialist cannot identify aprimary and secondary reviewer with the appropriate scientific or scholarly expertise, the IRB Specialist in consultation with the Director Office of IRB and HRPP arranges for expert consultation and will not place the protocol on an agenda until appropriate expertise is made available. 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 and secondary review responsibilities to another member who is appropriately qualified or obtain consultation from one or more experts outside the IRB (see below).

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 areknowledgeable about

or experienced in working with these participants (children, pregnant women, adults unable to consent, students, etc.). 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

The IRB Chair or IRB staff reviews the proposed convened meeting agenda and determines whether the IRB has the required expertise to review upcoming research. If not:

- The Director Office of IRB and HRPP, in consultation with the IRB Chair, will invite individuals with competence in the specific areas needed to assist in evaluating issues that require expertise beyond or in addition to that available on theIRB.
- 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 toallow them to conduct a thorough review. The documents are generally sent electronically, but paper copies could be mailed via the U.S. mail if needed.

When a consultant is used, that fact, and the pertinent information gained from theconsultant's assessment is uploaded in the iRIS electronic IRB system and available at the time of the protocol discussion at the convened IRB review, and recorded in the IRB minutes. The consultant must provide the IRB with a written report of his or her assessment which is kept with the protocolfile.

All consultants, internal or external to Geisinger, must comply with the IRB conflict of interest policy. They are not considered ad hoc IRB members, and cannot vote with the IRB members.

6.6 IRB Member, IRB Staff, and Consultant ConflictingInterest

*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. (**AAHRPP Element II.1.D**)*

Guidance – IRB Members on Conflicting Interests includes definitions of conflicting interest and outlines procedures for recusal. This policy applies:

- When protocols and reports (amendments, continuing review, final reports, etc.) are first received by members assigned to review
- During discussion and voting in convened meetings
- When consultants are asked to advise the IRB

IRB members and consultants with a conflict of interest:

- Are excluded from discussion except to provide information requested by the IRB.
- Are excluded from voting except to provide information requested by the IRB.
- Leave the meeting for discussion except to provide information (if requested) and voting.
- Are not counted towards quorum.
- IRB members with a conflict are documented in the minutes as being absent with an indication that a conflict of interest was the reason for the absence.

This applies to all projects reviewed by the IRB, regardless of whether the project is exempt or considered during full, expedited, or continuing review. This policy also applies to reviewsof non-compliance reports and Unanticipated Problems involving risks to participants or others.

IRB triage procedures consider conflicts of interest when assigning new protocols toan IRB, such as when any IRB member is named in the research protocol or has a relationshipwith the research, sponsor, or any research personnel.

See 45 CFR 46.107; 21 CFR 56.107.

IRB Member's Disclosure of a Conflicting Interest

All IRB members are required to complete an annual COI survey per Geisinger Policy 14.702 Geisinger Policy on Financial Conflicts of Interest in Research. Members who realize they have a conflicting interest when they are first assigned a protocol or report for review must notify the IRB staff or IRB Chair immediately so that the protocol can be reassigned.

IRB members review the draft Agenda before a convened meeting with the issue of conflicts in mind. The iRIS electronic IRB system automatically identifies those members who are also identified as study personnel by a red asterisk beside the study. Any conflicting interest for protocols to be voted on must be reported to the IRB Chair, Director, IRB Operations and HRPP, and/or IRB Specialist or Analyst before the meeting whenever possible.

If an IRB member realizes at a meeting that he/she may have a conflicting interest in a given project, then 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 Guidelines for IRB Members on Conflicting Interest 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.

Consultants 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 consultanthas been asked to provide information to the IRB, then the conflict of interest must be disclosed to the IRB members reviewing the protocol or present in the convened 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 room during discussion and voting.

IRB Staff and Conflicting Interest

IRB Staff must not participate in the review of research protocols, and must not make exempt determinations for research protocols in which they have a conflict of interest. IRB staff who realize they have a conflicting interest when they are assigned a protocol or report for review must notify their supervisor immediately so that the protocol can bereassigned. Also, IRB Staff are required to complete an annual COI survey per Geisinger Policy 14.702 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), may represent competing business interests, or be in a position to influence programmatic and budgetary decisions and exert undue influence on IRBs or individual IRB members. To avoid such influence on IRB determinations, the Chief Scientific Officer (CSO), and other Geisinger officers will not serve as voting members of the IRBs, 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 includespecific measures to manage any conflict of interest or the possibility of undue influence.

As stated in the charges to the IRBs, "…neither the CEO, CSO, 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.

To avoid any possible conflicting interests or influence on IRB determinations due to competing business interests, individuals who are responsible for development activities (including raising

funds), or are in a position to influence programmatic and budgetary decisions may not serve as IRB Members.

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**)*

The composition and membership of each IRB is evaluated annually by the Director, IRB Operations and HRPP with the IRB Chair(s) with input from the CSO and is adjusted asneeded to ensure: appropriate knowledge of applicable regulatory and legal requirements; knowledge of professional standards and practices; knowledge of the local research contextand 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 Chairs, and IRB staff is 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 IRB Member roster is maintained within the iRIS electronic IRB system and is used to maintain the IRB membership roster. Membership consists of at least five members, with varying backgrounds to promote complete and adequate review of research activities conducted at Geisinger. The iRIS electronic IRB system as well as a more detailed membership listing is kept within the IRB secured, shared computer network drive. The details include all information required under FDA and DHHS regulations and OHRP guidance (45 CFR 46.107 and 108; 21 CFR 56.107 and 108, including:

- Names of members
- Names of alternate members (and regular 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 generally alternate attendance and 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. Prior to a convened IRB meeting, the IRB Co-Chairs are in contact with the IRB staff and Director, IRB Operations and HRPP to resolve any questions or concerns to arrive at a consensus before the meetings begins. The IRB Co-Chairs attend monthly IRB Leadership meetings to share equal decisions and input on matters related to human research. 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 adequately protected.

Representative capacity is presented in enough detail to indicate which appropriate participants can be represented by each member (e.g., children, pregnant women). When research protocols include vulnerable participants, a member 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 immediatefamily, has any employment or other relationship (e.g., current employee, consultant, Board of Directors, current volunteer, trainee or student) with any of the Geisinger entity.

Changes in IRB membership require reporting to OHRP. The Director, IRB Operations and HRPP(or designee) submits a revised IRB membership list to OHRP per OHRP guidelines as appropriate.

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**)*

The IRB Chair/Co-Chairs are voting member of the IRB. The Chair(s), with the assistance of IRB staff, determines that a quorum has been established and maintained, chairs the meeting discussions, and calls for votes as appropriate. The IRB Co-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:

1. Quorum is a majority (one more than 50%) of the (voting) members of the IRB (or their designated alternates), including at least one member whose primary concern is in nonscientific areas, and one member whose primary concern is in scientific areas. A non-

scientist must be present to conduct a convened meeting. For research to be approved, the submission must receive the ***approval of a majority*** of such members present at the meeting.

2. ***Members may be present in person or through audio (telephone) or audio-visual teleconference***. All members have access to all meeting material. Laptops are available to all members at the meeting. All members can participate actively and equally in all discussions.

   All members, regardless of whether the members participate in person, or by audio or video conferencing, can participate fully in all IRB deliberations.

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

   - Total number voting
   - Number for
   - Number opposed
   - Number abstaining
   - Names of those recusing.

   Votes are indicated by voice vote and/or show of hands.

4. ***Members 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 protocol.

5. An ***individual who is not listed on the official IRB membership roster*** may not vote with the IRB.

6. A ***non-voting ex-officio member*** of, or representative to, the Geisinger IRB may not vote with the IRB.

7. ***Ad hoc consultants*** may not vote with the IRB.

8. A ***non-scientist*** attendance is always required for a meeting to begin and for any vote to be taken.

9. Regular attendance of ***unaffiliated*** members is expected. The unaffiliated members represent the general perspective of participants and are actively engaged and participate in IRB meetings. Individual members of the IRB may satisfy morethan one required type of member (i.e. a nonscientific member may also be the unaffiliated member).

10. ***When a member and his/her alternate both attend a meeting***, either person (but not both) may vote on each protocol.

11. ***Voting by proxy*** is not permitted.

12. ***If the quorum is not maintained during a meeting***, such as due to lack of a majority of

IRB members being present or an absence of a nonscientist member, the IRB cannot take any further actions or vote until the quorum is restored.

13. The ***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.

14. 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 participants.

Geisinger IRB is not constituted to review studies planning to enroll Prisoners per 45CFR46, Subpart C.

(See Section 8.3 – IRB Minutes) for 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 Element II.2.C**)*

The IRB meets twice a month according to a regular schedule.

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

Individual meetings may be rescheduled, or additional meetings may be held, as needed by agreement of the IRB Co-Chairs and the Director, IRB Operations and HRPP.

The deadline for receipt of research proposals is posted on the meeting schedule.

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 the iRIS electronic IRB system, which then makes available all necessary protocol materials to all members and reviewers.

Materials necessary for review may be presented to IRB members prior to a meeting only where determined necessary by the IRB Chair or Director, IRB Operations and HRPP.

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 Membersin 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 electronicallythat 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.

The Agenda details:

- Protocols that will be presented at the meeting,
- Protocols (new, minor modifications, or continuing reviews) that, since the previous convened meeting for this IRB, have been reviewed by the expedited or exempt process andrecommended for approval, and do not need to be presented at a convenedmeeting,
- 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 expiration date without prospective approval (continuing review).

7.2 IRB Study Applications

Geisinger IRB submissions are via a web-based 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
- Amendment/Modification Form
- Key Study Personnel Amendment/Modification Form
- Continuing Review Report Form
- Final Report Form
- Prompt Report Form – (Reports of unanticipated problems and events and information requiring prompt reporting to the IRB – this would include non-compliance)

Attempts have been made to avoid the 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 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 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*.

- Federally sponsored protocols submitted for exemption review must meet the requirements set forth in 45 CFR 46.104.
- Non-federally sponsored 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 or research participants and confidentiality of data as a condition for Exemption 2(iii) and 3(i)(C) 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, i.e., 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; 63 FR 60353-60356 DHHS-FDA list 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

Protocols: New protocols are submitted and received directly within the iRIS electronic IRB

system. Members of IRB staff triage all submissions. If submission documents appear complete (ensure all training; e.g. human research and COI, supplemental documents, and information is included) during the triage, the submissions are assigned to a member of the 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 PIas 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 the protocol review type, the order (by date) the protocol was submitted to the IRB, and for protocols subjectto convened review with assignment to the next IRB meeting.

Assignment to IRB: Amendment/Modification; Continuing Review Report; Unanticipated Problems; Non-Compliance and Final Reports:

If possible, all subsequent events submitted on approved protocols are pre-reviewed and assigned to the IRB Member reviewer who initially reviewed the protocol.

7.4 Protocol Review Material and Information

iRIS protocol submission forms 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 always include the iRIS study application and protocol. The study application may need to be amended with an Amendment/Modification Form if details outlined in the application change.

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
- 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 (drugs)
- Device manual or report of prior investigations (devices)
- Relevant external grant if required by sponsor
- All relevant reports, including multi-center trial reports (at continuing review)
- Biosketch for all study team members
- IBC approval, if applicable
- RSC approval, if applicable
- Signed billing determination, if applicable

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

7.5 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. *(See Section 6- Structure and Composition of the IRB).*

"Nonscientific" members assigned to review protocols are valued for the community perspective they bring to the process of ensuring the protection of research participants. For approved protocols an attempt is made to assign any subsequent protocol events to a member who was an assigned reviewer when the study was first approved.

IRB notification to organizational offices and officials

The Director, IRB Operations and HRPP reviews issues addressed in the minutes with the CAO during regularly scheduled meetings. The CAO meets regularly with the CSO who has opportunity to question.

Convened Review

The IRB uses the required criteria for approval for all reviews of research, including continuing review, and review of a modification to previously approved research when the modification affects a criterion for approval.

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 reviewerand secondary reviewer to present the protocol at the convened meeting. The primary reviewerconducts and 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 review all study submission materials. All reviewersreceive

an automated notification of the reviewer assignment within the electronic IRB system. All agenda materials are electronically distributed to all members at least one week prior to the meeting.

If the 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 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.

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. The reviewer reviews and presents the protocol at the convened meeting:

Major (or "Substantive") Modifications: A major (substantive) modification is one in which there is an increase in the level of risks to participants or a greater than minor modification inany 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 theconvened IRB

Substantive modifications or clarifications: These are requested by the convened IRB, and are directly relevant to required IRB determinations.

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. The reviewer reviews and presents the protocol at the convened meeting.

Reports (Unanticipated Problems and events and information requiring prompt reporting):
(See Section 3.10- Internal and External Reporting).

Expedited Review

See OHRP guidance Expedited Review Categories.

*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.**)*

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 documentsto conduct a thorough review of the submission. Assigned expedited reviewers must thoroughly review

all submission documents and materials as required for the convened IRBreview 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 uses the required criteria for approval for all reviews of research, including continuing review, and review of a modification to previously approved research when the modification affects a criterion for approval.

The evaluation by the assigned reviewer determines whether research undergoing initial review and continuing review 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 subjecttoconvenedreview initially) (Continuing Review Report Form
For a protocol initially subject to regular review, the continuing review submission undergoes expeditedreview:

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):

- 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 beenidentified.

Continuing Review(Protocols subject toexpeditedreview initially) (Continuing Review Report Form)

For a protocol initially subject to expedited review, the continuingreview 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 initialprotocol.

For continuing review of research, all IRB members, including the assigned reviewer has access to the entire protocol submission within the iRIS electronic IRB system, which includes the completeprotocol, 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 reviews are reported on the IRB agenda.

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 orothers
    - 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

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 approved on or after January 21, 2019 and ongoing studies that are minimal risk and did not already transition will be 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, status of participant interaction and research activities and the criteria outlined below. Removal of the continuing review

requirement will be communicated to the study PI in the Review Outcome Letter and documented in the study's electronic IRB record – Continuing Review and Expiration dates will be removed from the Study Outcome tab and Outcome letter.

If the IRB determines continuing review 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
- Research is eligible for expedite review in accordance with 45 CFR 46.110 with the following exceptions (per OHRP 2018 Requirements FAQs):
    - Where no subjects have been enrolled and no additional risks have been identified (expedited review category 8(b) - Studies that qualify for expedited category 8(b) 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.
    - Where (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 (expedited review category 9) – 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
- Accessing follow-up care from procedures that participants would undergo as part of clinical care.

☐ Additional criteria:

- FDA regulations do not apply to the study
- Study sponsor does not require continuing review
- No external institutions rely on GIRB for IRB review and ongoing oversight of their engagement in this study
- 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 history of serious or continuing research non-compliance or pattern of non-serious non-compliance

Protocols Qualifying for CIRB Review

Geisinger participates in the independent model of the National Cancer Institute (NCI) Central Institutional Review Board (CIRB) Initiative. Under this model, the Adult and Pediatric CIRBsare the IRBs of record for certain adult and pediatric national multi-center cooperative oncology group cancer treatment trials.

Currently, Geisinger provides information about local context to the CIRBs. The CIRBsassume responsibility for initial review, continuing review, modifications to approved research, Unanticipated Problems and non-compliance. Geisinger's role in this process is to oversee the local conduct of the research. The IRB maintains a current list of protocols reviewed by the NCI CIRBs. The Standard Operating Procedures for Adult and Pediatric NCI CIRB Ceded Research outlines submission and review requirements.

Final Reports

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

7.6 Protocol Review - Pre-Review

General Process for All Protocol Submissions

The IRB utilizes a pre-review process, which involves a preliminary review by IRB staff followed bya thorough review by IRB member reviewer(s). Protocols assigned to a convened meeting will be fully reviewed by the reviewer(s) prior to the meeting date to allow recommended changes (modifications) to the protocols to be made and questions answered before protocol presentation to IRB members at the convened meeting for final review and approval.

During the pre-review of a protocol, the IRB staff and reviewer(s) enter any comments or questions or recommended changes (modifications) to the protocol or associated documents (e.g. consent forms, advertisements, protocol, etc.) stemming from the review into the iRIS reviewer sheet, stipulations/recommendations.

7.7 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 voting 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 should be considered a nonscientist. Expert reviewers/consultants are not required to attend the convened meeting; however, they must provide a written overview of the study. There may be times when the IRB may invite them to attend; however, they do not vote.

Materials Available at Convened Meetings

Prior to the convened meeting, all scheduled voting IRB members, including non-primaryand secondary reviewers, are notified electronically that agenda and all meeting materials are ready to review. This electronic access enables reviewers to see all the details of the protocol submission, including the study submission and any reports (e.g. modification, continuing review, reportable events), all comments and responses, assent and consent form(s) and all other documentsassociated with the protocol (e.g. telephone script, questionnaires or surveys, advertisements). Reviewersare expected to review the information sufficiently to provide comments (if any) before the meeting and during the meeting. All materials submitted supporting a protocol are also available to voting members during the meeting.

The meeting agenda, which includes a list of protocol approvals (all protocols reviewed for that meeting period, including protocols approved by expedited review and protocols reviewed by exempt review), as well as educational and informational items being presented, is available for all members to review and prepare for discussion at the meeting.

Meeting Deliberations

The primary and secondary reviewers are considered the lead reviewers on the IRB for protocols assigned to them. 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 toolsas guidance.

The primary and secondary reviewers are designated as the presenters who present the protocol for discussion at the convened meeting. All IRB members have an opportunity to discuss each research protocol during the convened IRB meeting. The members and reviewers consider the approval criteria set forth in 45 CFR 46 and 21 CFR 50 in reviewing a protocol. The IRB confirms the proposed study submission, informed consent documents, protocol, and recruitment documents are accurate and complete. Controverted issues that have not been resolved during the review prior to the convened IRB meeting are discussed.

Range of Actions on Protocol Review at Convened Meetings

The convened IRB must systematically evaluate each protocol to ensure the protection of research participants and reach a decision.

Review Actions

Regardless of the submission type (initial review, continuing review, amendment/modification review, etc.), the possible decisions by vote of a majority of the convened IRB (quorum) may take one of the following review actions when reviewing the submission.

- *Approve with no changes:* (or no additional 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 will 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 official 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 a formal approval letter is sent to the PI after the IRB staff in consultation with the IRB reviewer or chairperson (or any other individual(s) designated by the IRB) and the response has reviewed and accepted as satisfactory all changes to the protocol or informed consent documents or any other responsive materials, required by the IRB from the investigator. This review is carried out via an administrative review process.
- *Deferred (Tabled):* The convened IRB determined that submission may be approvable but required greater than minor (substantive) changes or requirements, requests for more information for IRB consideration, and other issues related to the criteria for approval require review and approval by the convened IRB to meet the approval criteria and the study submission. The submission must be re-reviewed by the convened IRB. The research may proceed only after the convened IRB has reviewed and approved the Review Response with required changes to the research. 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 adeferred protocol is reviewed, additional reviewers will be assigned to review and presentthe 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., the regulatory requirements, Geisinger HRPP standards, or other stipulations have not been satisfied). The investigator and study contact are provided with a formal letter notifying them 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 in person or in writing.

Continuing review by the convened IRB includes a thorough review of information in the Continuing Review Report Form, which provides a detailed status report on the progress of the research including the following:

- A summary since the last IRB review of:
  - Current enrollment status
  - Status of participant interaction and study activity
  - Serious Adverse 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

The review also includes a review of the iRIS study file that contains a complete history of all study activity, reports, and approval.

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

Approval Date and Determination of Expiration Date

The approval date for a protocol subject to either initial or continuing convened review is the dateof the IRB meeting at which the protocol was approved. The IRB could 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 orany 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 beingaddressed.

For example:

- 12/1/14 – convened review date requiring minor modifications
- 1/1/15 – administrative review with approval acknowledging all changes were made
- Approval date 1/1/15 – Expiration date 11/30/15

Approval contingent on substantive changes or requirements, requests for more information forIRB consideration, orotherissues related tothe criteria forapproval 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 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
- Approval date 12/1/14 – 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 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.

(The IRB does not consider this a suspension or termination under See *Section 9.3- Risks to Vulnerable Populations*, since it is no activity under an "approved" protocol.)

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 thebest interests of each 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 study submission system, "iRIS" and all submission documents except Compliance Audits are maintained electronically within the iRIS electronic IRB system and are accessible by all members of the study team and all IRB members and at any time.

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, and/or 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, review type, meeting date, sponsor, reviewer or any combination of the above categories. Electronic copies of all submission materials, 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.

A protocol file contains the following, as applicable to the research:

1. **Study Application** - Submitted for all human research projects.
2. **Protocol** – Submitted for all studies. Could include sponsor's protocol or if investigator initiated, a copy of the either the retrospective or prospective protocol.
3. **Biosketches or CV's** – Submitted for all members of the study team.
4. **Amendment/Modification Form** - Submitted for modifications to already approved research.
5. **Key Study Personnel Amendment Form** – Submitted for modifications to study personnel.
6. **Continuing Review Report Form** - Submitted for continuing review of research.
7. **Prompt Report Form** - Submitted for reportable events and information (that would include both unanticipated problems and non-compliance)
8. **Final Report Form -** Submitted for closing protocols.
9. **Reports of injuries to participants –** Generally included with Unanticipated Events Reporting.
10. **Significant new findings –** Submitted with Unanticipated Events, Continuing Review of Amendment/Modification reporting.
11. **The informed consent document(s) -** The protocol file includes all versions of the consent form, including the currently approved consent form. When a sample consent form(s) from sponsors are provided, they are included in the protocol file.

12. **The Assent form(s) -** If a study involves children from whom the investigators will obtain assent, copies of all versions of the assent form, including the currently approved assent forms will be included in the protocol file**.**
13. **Scientific evaluations of the proposed research** - Documentation of scientific review by the SRC is included in the protocol file. (See Section 1.7- Scientific and Scholarly Validity Review and Ethics Review) for information on scientific and scholarly review.
14. **Sponsor Materials -** For investigational drug studies, the Investigator's Brochure and Sponsor's Protocol, including current amended editions of these documents and all previous versions are included in the protocol file.
15. **FDA Letters –** Copies of FDA approval for of IND and IDE, etc. as applicable.
16. **Grant Application and Award Notice** - For research supported by an external grant, a copy of the grant application and award notice must be in the protocol file if required by sponsor.
17. **Billing Determination and Schema** – For all research with billable patient events.
18. **Advertisements phone screening scripts** and non-medical oral scripts, flyers, website or other subject recruitment materials.
19. **Questionnaires, surveys, interview scripts, diaries** or other documents used during the study.
20. **Participant informational sheets,** brochures and sponsor newsletters.
21. **Reports submitted for reportable events and information per** Guidance – Prompt Event Reporting to the IRB.
22. **Data and Safety Monitoring Board (DSMB) reports,** Annual Progress reports – Submitted with the continuing review report if no additional risks or safety issues identified.
23. **Conflict of Interest (COI) documents** and/or reporting when COI is applicable.
24. **Correspondence and communication** between IRB staff, IRB reviewers, IRB members, and investigators and study team members**.**
25. **Other IRB correspondence** related to the research**.**
26. **Documentation of all actions** including approvals, disapprovals, waivers or alterations of consents and HIPAA authorizations (as documented in the study submission forms).
27. **Letters (including Approval letters, Recommendation for Modification, Deferrable, or Notice of Exempt Review)** for research subject to exempt review.
28. **Documentation of protocol closeout if any, including Final Report Form.**
29. **All Reminder Notices,** including Expiration notice.
30. **IRB approvals from collaborating institutions** are requested and included in the research file. IRB approval notices are requested from collaborating institutions when Geisinger is the coordinating center for a multi-site study, or when data is being received at Geisinger. If the study is a multi-site study, with Geisinger as one of several participants, no other IRB approval is gathered or included from other participating sites.
31. **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.
32. **IRB Documentation** – Record of initial and continuing review of research by the expedited review procedure including:
    a. Justification for using the expedited procedure

b. Rationale for requiring ongoing continuing review when the study otherwise meets criteria for removing the requirement for continuing review
c. Actions taken by the reviewer
d. 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 that has been found to ***not*** meet the definition of 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 each IRB Member including; contact information, background and experience, curriculum vitae, etc.

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 or as hard copy in the IRB storage room. Periodically, these documents are transferred to another site for long-term storage.

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 sent for long-term storage. Access to those materials can generally be obtained in 48 hours, or less, 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 access.

Access to IRB records is routinely provided to the IRB Chairs, 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 foraccess 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 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 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 minutes document:

- Meeting attendees and invitees, including IRB members, alternate members, ex-officio members, guests, and staff
- 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 alongwith 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 thatjustify those determinations
- If disapproved, the basis for disapproving the research
- Votes for each action recorded as numbers for, against, or abstaining
- 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 bydocumenting:

- The IRB members (voting, non-voting, and ex-officio) who are inattendance
- Each attending member's mode of attendance – in person or via telephone
- When an alternate member replaces a primary member and voting atthe convened meeting
- The continued presence of quorum for all votes, including a member whose primary

concern is in a nonscientific area
- All members may actively and equally participate in all discussions. All meeting materials are available to all members regardless of attendance at the meeting.
- 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, and consultants)

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, such as:

- Discussion of protocol events – new, continuing review, amendment/modifications, reports of Unanticipated Problems and events and information requiring prompt review, non-compliance, and final reports

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, (and if appropriate to the degree of risk determination of an approval period of less than one year)
- Approval of research contingent on specific minor conditions, and the designee (staff or IRB member) appointed to sign off on the condition when met. 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.
- 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
  - Guidance – IRB Review of Medical Device Research
- Approval of waiver or alteration of informed consent, pursuant to:
  - 45 CFR 46.116(c) and 45 CFR 46.116(d)
- Waiver of informed consent documentation, pursuant to:
  - 45 CFR 46.117(c) and 21 CFR 56.109(c) (1)
- Research involving adults with impaired decision-making
- Waiver of HIPAA Authorization, pursuant to
  - 45 CFR 164.512(i) (2) (ii)
- Waiver of HIPAA Authorization for recruitment or screening, pursuant to
  - 45 CFR 164.512(i) (2) (ii)
- Alteration of HIPAA Authorization, pursuant to
  - 45 CFR 164.512(i) (2) (ii)
- Use of short form process for consent:
  - 45 CFR 46.117(b) (2) or 21 CFR 50.27(b) (2)
- When research involves children, the following IRB decisions are documented:
  - Appropriate children finding applicable to research:
    - OHRP - 45 CFR 46.404, 45 CFR 46.405, 45 CFR 46.406, 45 CFR 46.407, 45 CFR 46.408
    - FDA - 21 CFR 50.51, 21 CFR 50.52, 21 CFR 50.53, 21 CFR 50.54,

21 CFR 50.55

- Whether the permission of one parent/guardian is sufficient or if permission from both parents/guardians is required. (See Guidance Parental Permission)
- How assent is to be solicited or obtained, unless waived.
- The participation of children who are wards of the state is approved under:
  - 45 CFR 46.406, 45 CFR 46.407 only if 45 CFR 46.409(a) is satisfied, or
  - 21 CFR 50.53, 21 CFR 50.54 only if 21 CFR 50.56(a) is satisfied

- Appropriate involvement of pregnant women, fetuses, and neonates pursuant to:
  - 45 CFR 46.204, 45 CFR 46.205, 45 CFR 46.206, and 45 CFR 46.207
- Approval of research involving prisoners as participants under the following regulations:
  - *45 CFR 46.305 and 45 CFR 46.306 – *Currently Geisinger does not conduct prisoner research. If prisoner research were to be done the membership would be modified accordingly.*
- Determination of the level of risk
- Determinations of serious or continuing non-compliance
- Unanticipated Problems

Other Issues

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

- Other events and information that require prompt reporting to the IRB (See Guidance – Prompt Event Reporting to the IRB).
- DSMB reports if not part of the continuing review report
- Approval of minutes of prior convened IRB meetings
- The approval of research contingent on specific minor conditions by the chair or designee, in the minutes of the first IRB meeting that takes place after the date of the approval
- Presentation of information from an outside consultant or expert as previously requested by the IRB
- Special situations such as use of a test article and humanitarian use devices
- The names of IRB members who abstain for reasons other than conflict of interest
- Educational training
- Other items as applicable

Disposition of the IRB Minutes

The IRB staff members compose the minutes and make them available for IRB review - generally by the next meeting date. Minutes may not be altered by anyone including a higher authority once approved by the members at a subsequent convened IRB 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 & HRPP.

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**)*

When reviewing the study submission, the IRB analyzes and assesses levels of risk, ensures risks are minimized, and ensures risks are reasonable relative to anticipated benefits, beforeapproving the proposed research. *(See Section 14.3- Detection of Harm, Minimization of Risks and Mitigation of Potential Injuries*)

HRPP policies are based on both the Common Rule 45CFR46.111 and FDA 21 CFR56.111.

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.

DEFINITONS:

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(j)]. 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 andAnalyzingPotential Risks

The PI must 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 arenecessary:
  - i ensure necessary medical or counselling intervention in the event of harm to participants
  - ii 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.

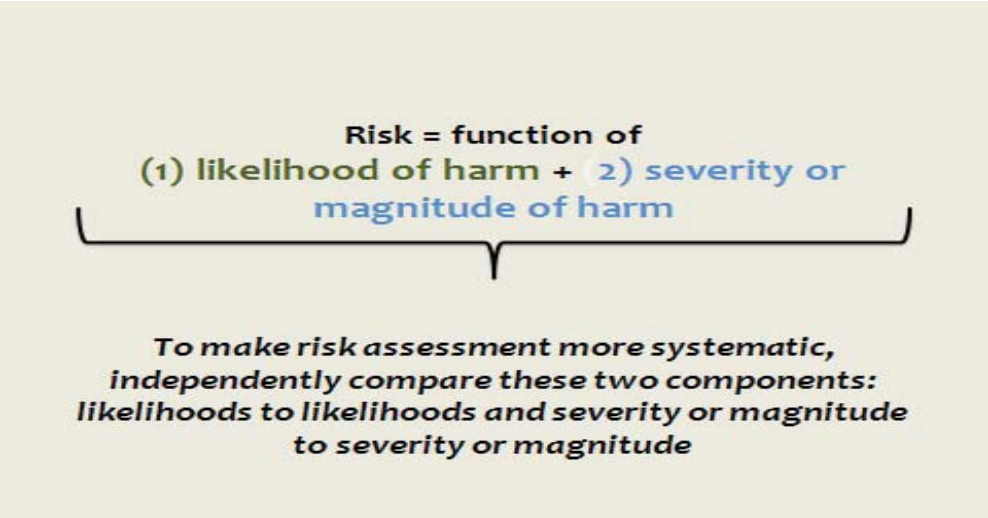
When proposing changes to the research, PIs must submit an Amendment/Modification form describing the proposed changes and explaining the impact on the level of risk and potential benefits.

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, 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. [45 CFR 46.111 21 CFR 56.111 (a) (1) (i)]

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

Figure 1

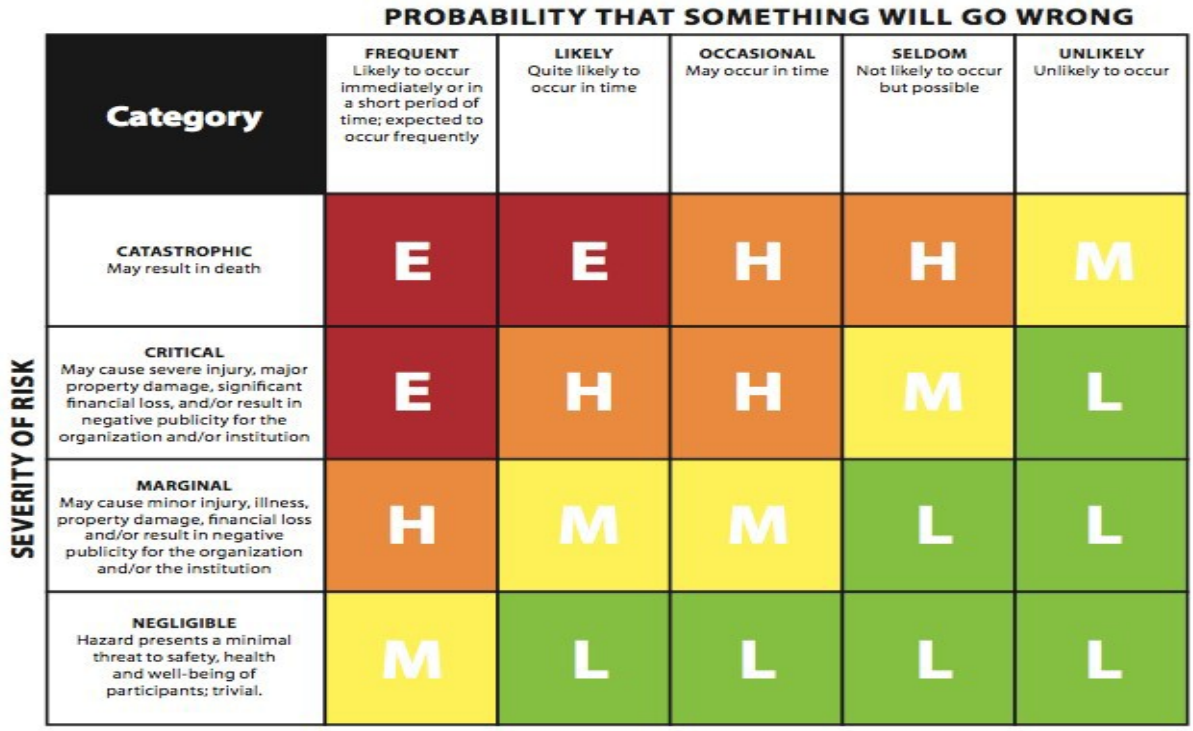


Before approving a research protocol, the IRB must determine that risks are minimized as follows by:

- 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, for example: having an adequate data monitoring plan, or protecting confidentiality by using coded data. If risks are not adequately minimized, the protocol will not be approved as written. See 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 ensures adequate resources during the submission to the IRB under Geisinger Investigator Assurance.

(See Section 14.3- Detection of Harm, Minimization of Risks and Mitigation of Potential Injuries) for additional guidance information.

Risks v. Anticipated Benefits

The study submission requires that the PI describe the anticipated benefit(s) that may be gained by participants, and how the knowledge gained may benefit the participants, future participants or society. The PI must 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 mayreasonably be expected to result. [45 CFR 46.111, 21 CFR 56.111(a) (2)]

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 notparticipating 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 planmakes adequate provisions for monitoring the data to ensure the safety of research participants. (45 CFR 46.111, 21 CFR 56.111(a) (6))

More than minimal risk studies need a Data Monitoring Plan outlined:

- 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 or DMC (a data safety monitoring board, or committee – the terms are generally used interchangeably): for example, 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 monitoring plan for Phase I or Phase II studies generally can be done by the study team.

The data monitoring for minimal risk studies generally involves 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 or are not required to 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 that trigger an immediate suspension of the research, if applicable.

PIs are required to describe a Data Monitoring Plan, if applicable, in the Study submission. See: Guidance Data and Safety Monitoring - for detailed information on what a data monitoring plan might address, when a data monitoring plan is required, and whena data monitoring board or committee is required.

- Section 15 - discusses PI responsibilities
- Data Monitoring Committees - FDA March 2006 "Guidance for Clinical Trial Sponsors"
- 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
  - NCI: Data and Safety Monitoring Guidelines: Essential Elements

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 including a summary of adverse events, 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 ayear (for studies with a continuing review requirement), if they determine 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 Common Rule require IRBs to give special consideration to protecting the welfare of vulnerable participants.

To approve research involving vulnerable populations, the IRB follows and 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 (45 CFR 46 Subpart D; 21 CFR 50 Subpart D),
- Pregnant women, human fetuses, or neonates (45 CFR 46 Subpart B),
- Persons with impaired decision-making, or
- Economically or educationally disadvantaged persons
- Employees

The IRB determines whether the criteria for approval of research are met when research involves nonviable neonates. The Pediatric representative of the IRB determines and documents the following:

- Where scientifically appropriate, preclinical and clinical studies have been conducted and provided data for assessing potential risks to neonates.
- Individuals engaged in the research have no part in determining the viability of a neonate.
- Vital functions of the neonate are not artificially maintained.
- The research will not terminate the heartbeat or respiration of the neonate.
- There is no added risk to the neonate resulting from the research.
- The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.

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 Section 12) often address issues related to competency to consent for research, emancipated minors, LARs, 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. When weighing the decision whether to approve or

disapprove research involving vulnerable participants, the IRB verifies that such procedures are a part of the research plan. 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 on the recruitment of vulnerable populationssee:

- Observation of the Consenting Process
- Guidance Recruitment
- Section 14.4

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.

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 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 generally 18, but there are important exceptions

Limits on IRB Exemption and Exempt Review 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:

1) Minimal Risk Research

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:

- Is reviewed pursuant to 45 CFR 46.404, and pursuant to 21 CFR 50.51 if an FDA-regulated product is involved;
- Presents only minimal risk to the children who are enrolled; and
- Provides adequately 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.

2) Research with More than Minimal Risk that Presents Prospect of Direct Benefit to Participants

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:

- Is being reviewed pursuant to 45 CFR 46.405 and pursuant to 21 CFR 50.52 if an FDA regulated product is involved;
- Poses risk to the subjects that is justified by the anticipated benefit to the subject;
- 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
- 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 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

To approve this type of research protocol, the Geisinger IRB must determine, and document in its meeting minutes and/or review documents, that:

- 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;
- That the risk of the research protocol is just a minor increase over minimal risk;
- 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;
- 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 That the research protocol provides

adequately 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.

4) 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

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.

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:

- 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.
- 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.
- That the research protocol provides adequately 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. 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 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 and 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 and reviewed by the IRB and modified by the PI if required by the IRB.
- Relevant IRB minutes and correspondence.

OHRP and FDA Approval of 407 Research that is Federally Supported

Expert panels established by OHRP and FDA (if a 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 407 Research

If the IRB finds that research that is not subject to HHS jurisdiction and 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.

Decisionally Impaired Participants

The IRB reviews the risk-benefit analysis including the possibilities of coercion and undue influence, and must determine whether such participants 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 decisionally impaired participants 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. [45 CFR 46, Subpart B.]

Under these regulations, the IRB is required to document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent, in accordance with the Guidance - Research Involving Pregnant Women, Fetuses, and Neonates.

In general, Subpart B 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, each with their own requirements and IRB determinations, apply to research with pregnant women, human fetuses, and neonates:

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 45 CFR 46, Subpart D, which is discussed later in this section.
    - *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, research involving these participants is socially important for understanding and eventually improving adverse health and general well-being in 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 andundue influence. The IRB has the same standards for approving research involving these groups as other vulnerable participants.

Prisoners

Geisinger IRB is not constituted to review studies planning to enroll Prisoners per 45CFR46, Subpart C. 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 (45 CFR 46.113; 21 CFR 56.113) to suspend or terminate a previously approved protocol.

DEFINITONS:

Suspension: Temporary withdrawal of IRB approval for some or all research procedures in a protocol or the permanent withdrawal of IRB approval of part of a protocol. Continuing review of the research is still required. A sponsor-imposed suspension alone does not constitute sucha 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 sucha suspension (but may need to be submitted to the IRB as a protocol amendment/modification).

Termination: Permanent withdrawal of IRB approval of a previously approved protocol.

Suspension or Termination by the IRB

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 IRBrequirements
- Unexpected serious harm to subjects.

The IRB Chair has the authority to temporarily suspend or terminate research on an urgentbasis 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.

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 the Chief Scientific Officer and others in accordance with the procedure set forth in Section 3.9.

The PI shall be provided with an opportunity to 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
- Describe any monitoring and follow-up for safety reasons that will be conducted
- 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 for review and approval of the IRB or its designee of all communications by the PI to participants about the IRB action
- 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 andSelection

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

- Section 14.4 - Recruitment
- Guidance - Advertisements Appropriate Language for RecruitmentMaterial

PIs are directed to enter detailed information on how participants will be identified and recruited in response to questions in the Study submission. PIs are required to identify the target populations (including age range, gender, and ethnic background), the inclusion and exclusion criteria and whether payments will be made for participation. In addition, PIs are requiredto justify the inclusion of targeted persons (e.g., healthy participants, employees, students or participants with certain medical conditions). In determining if the selection and recruitmentof 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 the influence of 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 the recruitment and selection strategies are fair, equitable, and not misleading. If recruitment strategies fail to meetthese 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, and homeless people. The PI must substantiate his/her decision to involve 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 tothese populations. While pregnant women are considered vulnerable participants, women of reproductive age should not be arbitrarily excluded from participation in research. If womenare to be excluded, such exclusion must be fully justified by the PI based on scientific rationale. The IRB adheres to 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

PIs are required to provide details on all methods of recruitment proposed on a project, including how participants will be identified for recruitment. Guidance on recruitment is available. 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 (flyers, radio, newspaper, or internet) and information contained in the advertisement must be approved by theIRB.

- *Audio and video tape:* The IRB may review and approve the wording prior to taping to preclude re-taping due to inappropriate wording. The IRB reviews the final version of the advertisement.
- *Printed advertisement developed by Geising er research staff:* Printed advertisement that is visible to Geisinger patients must first be reviewed and approved by Geisinger's Corporate Communications. Confirmation of review of the advertisement must be included with the protocol submission to the IRB for final review and approval.
- *Printed advertisement developed by clinical sponsors:* Printed advertisement that is visible to Geisinger patients must first included with the protocol submission to the IRB for review and approval.

Also see:

- Section 14.4 Recruitment
- Guidance - Advertisements: Appropriate Language for RecruitmentMaterial
- Recruiting Study Subjects [FDA]

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 Guidance Payment – Ethical Considerations.

Geisinger Policy 14.313- 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 notallowed:

- 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 liabilityfor negligence.

Payment Arrangement among Sponsors/Organizations, Investigatorsand 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 otherpolicies referenced in this section, to protect participant privacy and dataconfidentiality.

In order to approve research or determine research meets the criteria for exemption under categories 2(iii) and 3(i)(C) under *Geisinger 2018 New Rule* (adapted from 45 CFR 46.104, 109), 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) and 21 CFR 56.111(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 provided by the PI in the Study submission, and assesses the amount and type of private information involved, how the information will be collected, and plans for its use, storage and disclosure. As necessary, the IRB will ask for additional details during its review.

DEFINTIONS:

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.

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 thatare inconsistent with the understanding of the original disclosure. In the context of a research protocol, "confidentiality" refers to the understanding between the participant andinvestigator (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 takingplace
- Which has been provided for specific purposes by an individual and whichthe individual can reasonably expect will not be made public (for example, amedical record).

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

- Sexual attitudes, preferences or practices.
- Use or treatment for 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 psychological or mental health.

Protected Health Information (PHI) is defined in the HIPAA privacy regulations in 45 CFR 164.501 and in the 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

PHI that is either transmitted by electronic media or maintained in electronic media is referred to as electronic protected health information, or ePHI.

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 and at convened meetings. 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 setting with other than a health care provider or in other than a private clinical 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**)*

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.

As a condition of protocol approval or determine research meets the criteria for exemption under categories 2(iii) and 3(i)(C) under HHS Final Rule (2018 Revised Common Rule) (45 CFR 46.104, 109), an IRB member conducts "limited review" and determines that there are adequate provisions to protect confidentiality of information related to potential or current participants, throughout the research, including data analysis and retention. PIs are expected to design studies to maximize confidentiality to avoid unintentional and unauthorized release or other disclosures.

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 and at convened meetings. The IRB may ask for additional details during its review, depending on the sensitivity of the information being used, maintained or disclosed. Generally, the greater the sensitivity of the information, the more stringent the security measures that are 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.

It 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. See the Study Submission Checklist for the information requested by the IRB for this assessment.

For active protocols, any changes in confidentiality protection measures must be described in either an amendment/modification form, revised study submission, and 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 Geisingersecurity policies to protect the confidentiality of the information collected under a protocol.

Geisinger has guidelines for best practices for maintaining confidentiality. The Geisinger HIPAA privacy policies including best practices for:

- Protecting PHI against public viewing;
- Storage and disposal of documents that contain PHI;
- Safeguarding computer workstations and databases that access PHI;
- Faxing and emailing PHI

Techniques described in these policies may be generally applied to all information.

Researchers must obtain Privacy Office/Information Security Review/Risk Assessment when electronically sending data outside of Geisinger. The Risk Assessment must be included in the IRB submission. The IRB staff may consult with the Geisinger's Privacy Office, or Information Security Office (ISO) as needed.

Geisinger provides appropriate security on all devices and networks. The IRB reviews specific details as to how the PI handles data to assure appropriate protections.

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 continue to 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 more information about CoC, PIs may consult with IRB staff and visit theNIH CoC kiosk.

Confidentiality Protections – During Data Analysis, Dissemination and Retention

Research performed at Geisinger generally uses a combined consent/authorization form, 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 Guidance - Retention of and Access to Research Data, and should refer to this guidance when considering the disposal of identifiable data and/or specimens.

PIs 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

In accordance with HIPAA regulations [45 CFR 160 and 45 CFR 164], the IRB serves asthe Privacy Board and oversees compliance with some of those requirements 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. In accordance with the HIPAA privacy regulations, Geisinger has approved and posted and the IRB adheres to a HIPAA policy specifically governing research Policy 09.105 – Research Permitted Use and Disclosure of PHI for Research.

The policy describes under which circumstances protected health information (PHI) may be accessed and used or disclosed for research purposes.

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 has designated a Privacy Officer to coordinate HIPAA activities throughoutthe system.

11.4 Confidentiality Breach - Unauthorized Release ofInformation

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. It follows the process set forth in Section 3, in order to review and respond to the situation.

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 the Geisinger Privacy Office Geisinger Policy 09.06.060, *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. (AAHRPP Element II.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. 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 generally 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 writtenconsent document;
4. Ongoing discussions between the investigator and/or members of the study team and the participant regarding matters related to continued participation in thestudy.

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 culturallyand 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. Underthis

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 andconfidentiality 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.

Refer to Section 14.6 for more information on the consent document, and principal investigator responsibilities in the informed consent process.

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 orundue 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. Periodic consent form reviews comparing signed and dated consent forms with the IRB-approved versions, which is monitored by ORC.
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 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 or not 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 particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
- 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 must 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 in HHS Final Rule (2018 Revised Common Rule)*:*

- 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 might be 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 addressedin Section 12.2.

Additional Consent 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 I.1.G**)*

The IRB can consult with the Legal Services to aid investigators and the IRB in understanding, applying and resolving any conflicts among applicable laws.

Required Signatures: The informed consent document must be signed and dated by the subject or the subject's LAR, the person obtaining consent and witness, when applicable.

A copy of the informed consent document will be given to the subject.

When the consent document includes HIPAA authorization, a copy of the signed and dated consent document will be given to the subject.

Adequate opportunity: The investigator and/or member of the study team will give either the subject adequate opportunity to read the consent document before it is signed.

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. See Guidance – Informed Consent & HIPAA Authorization – Required Elements.

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 anauthorization 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 Consent/Authorization templates that incorporate HIPAA authorization and Research Consent language are provided on the HRPP website.

If the ICF includes **HIPAA authorization** (or if stand-alone authorization is used, the following elements are required:

- 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 (or AtlantiCare) 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 or AtlantiCare [select appropriate one] 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 which we apply to (PA: "CONFIDENTIALITY OF HIV-RELATED INFORMATION ACT" Act of 1990, P.L. 585, No. 148 PA Act 148; Comparison of Pennsylvania Confidentiality of HIV-Related Information Act (Act 148); Federal Health Insurance Portability and Accountability Act)

If the research protocol includes testing for HIV, separate clinical HIV testing consent processes must be followed in accordance with PA Act 148.

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

The 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 withthe 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 bemet:

- 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 and iRIS Help area provide consent form templates, including 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 toinvestigators 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 determinesthat:

- 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 alteration of consent is approved by the IRB. 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 documents for investigators' use: *Short Form Consent – English Translation* and *Short Form Consent – Spanish*.

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 thesubject 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 anencrypted 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

*(Also addresses portions of **AAHRPP Element II.4.A**)*

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, suchas 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 for research involving pregnant women, fetuses, and neonates (45 CFR 46, Subpart B), and children (45 CFR 46, Subpart D and 21 CFR 50 Subpart D and special considerations for providing legally effective informed consent for these participants. *(See Section 9.3-Risks to Vulnerable Populations)* concerning determination of the risks to vulnerable populations as defined in applicable federal regulations, and specifically for determining the required risk categories in protocols involving children and prisoners.

The IRB determines whether the approval criteria for consent and permission are met when research involves pregnant women or fetuses. 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 orneonate.

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 has 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.

Adults with Impaired Decision-Making Capacity – "Decisionally Impaired"

*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 unableto:

- 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 otherperson.

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 legallyauthorized representative (LAR). If planning to enroll participants with diminished capacity, the investigator

must develop a plan to determine whether or not the prospective adult participant has the capacity to consent and if they do not, whether or not 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 jurisdiction in which the research is conducted (e.g., local or state law). Most states, including Pennsylvania, don't 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 generally 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 anindividual 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 must 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 must 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.

Consent with LAR

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; 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 should 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. 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:

1. 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".
2. 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.
3. 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.
4. In the presence of the witness, the signatory will ask the prospective study participant, if they agree to participate in the research study.
5. 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.
6. 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.
7. The signatory will then sign their name on the line provided on the "Consent Form Addendum for Patients Unable to Sign the Consent Form".
8. The witness will sign the "Consent Form Addendum for Patients Unable to Sign the Consent Form" on the line indicated for the witness.
9. 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 theconsent 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 OHRP, the IRB requires that additional protections be provided to pregnant women, fetuses and neonates involved in research. General considerations related toresearch involving pregnant women, fetuses and neonates are set out in Section 9. The special informed consent requirements are specified in 45 CFR 46, Subpart B and are summarized inthe Guidance - Research Involving Pregnant Women, Fetuses, and Neonates.

Nonviable Neonates

Consent may not be obtained from a LAR of either or both parents of anonviable neonate. The IRB will not permit elements of the informed consent process to be altered or waived in research involving nonviable neonates, even if the general requirements for waiver are satisfied.

When it has been determined that the neonate is viable, the neonate is considered a child and the consent requirements laid out 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 45 CFR 46, Subpart D and 21 CFR 50, Subpart D.

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, a person under 18 years old is considered a "child," and may not legally give consent, although there are certain exceptions for emancipated and self-sufficient minors.

Since children cannot legally give consent, informed consent must be obtained from parents ("parental permission") or the legally appointed guardian. The IRB requires the investigatorto 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 basic 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 (45CFR46.404 and 405)

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 (45CFR46.406 and 407)

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	1 parent/guardian	45CFR 46.404 / 21CFR50.51
More than minimal risk / direct prospect of benefits to child	1 parent/guardian	45CFR 46.405 / 21CFR50.52
More than minimal risk / NO direct prospect of benefits to child	2 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; and
- 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. Generally, children aged 7 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 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 generally 18, but there are important exceptions.

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

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 begranted are discussed in the Guidance Consent for Protocols Involving Children and Consenting Minors.

See guidance documents:

- Consent for Protocols Involving Children and Consenting Minors
- Parental Permission
- Section 12.4 for information on documentation of informed consent, and assent

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.

Illiterate Participants

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)

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 going through 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 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 toparticipants.

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 Section 14.6 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 whetherthe informed consent process will be appropriately conducted given the protocol-specific

circumstances (e.g., level of risk, inclusion of special participant populations) andadequately protects participants, considering issues such aswhether:

1. Participants have sufficient time to discuss concerns and decide whether to participate in the research;
2. The possibility of coercion and undue influence isminimized;
3. Communications to the participant or his/her LAR are in a language understandable to them; and
4. 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 consentdocument, must be satisfied for IRB approval.

The IRB may require revisions to the consent document as a condition for approval. Ifthe 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). *(See Section 14.6- Human Research Protection Resources*)

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. (**AAHRPP Element II.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 eight basic elementsof informed consent and the six additional elements of informed consent, when appropriate (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 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 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 *Section 12.1- Requirements for Informed Consent* for additional information. Only the IRB approved informed consent document may be used, and unlessthe 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. FDAregulations require that the signature be dated.

To facilitate accurate billing for clinical care incurred within the context of a research study, Geisinger requires the addition of the unique study-specific research diagnosis to the patient's problem list within the electronic health record at the time of consent for all patients enrolled in clinical trials and clinical research studies with clinical charges.

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. (**AAHRPP Element II.3.G**)*

Under HHS 45 CFR 46.116, IRBs have authority to alter or waive the requirement to obtain informed consent.

FDAregulations(overseeing clinicalresearchstudiesinvestigationaltestarticles, i.e. drugs and/or devices – IND and IDE) do not provide for a waiver or alteration of the informed consent process; the only exceptions to the informed consent requirements are for clearly defined circumstances of emergency use of a test article (see Section 5.7-Other Access to Investigational Drugs and/or Devices), and waivers granted for planned emergency research (see Section 12.6). Thus, the information in Section 12.5 only applies to non-FDA-regulated research.

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:

1. The research involves no more than minimal risk to the subjects;
2. The research could not practicably be carried out without the requested waiver or alteration;
3. If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
4. The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
5. Whenever appropriate, subjects will be provided with additional pertinentinformation after participation.

Special Considerationsfor 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 requestto 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 IRBmay 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 stillmust 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 detailsoutlined.

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 determinethe regulatory basis for the waiver as one of the following:

(a) Under OHRP (45 CFR 46.117) the IRB must find and documenteither:
   i. 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

(b) 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)).

Guidance Findings for Waiver or Alteration of Consent Documentation is available to IRB members and on the Human Subjects Researchwebsite.

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):

A. The use or disclosure of protected health information (PHI) involves no more than minimal risk to the privacy of individuals based on;
   1. An adequate plan to protect the identifiers from improper use and disclosure;
   2. An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law;and
   3. Adequate written assurances that the protected health information will not be 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 use ordisclosure of protected health information would be permitted by the Privacy Rule;

B. The research could not be practically conducted without the waiver or alteration; and
C. The research could not be practically conducted without access to and use of the protected health information.

See Geisinger "Policy 09.105 Research Permitted Use and Disclosure of PHI for Research".

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. (AAHRPP Element II.4.C)

Note: "Planned emergency research" ***is not synonymous with*** "emergency use of a test article", which is addressed in Section 5.7.

Planned emergency research refers to research planned for emergency settings, including the planned use of a test article.

Planned emergency research involves an extensive approval process, including FDAapproval, 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 LARis not available.

The IRB may waive the requirement for informed consent in accordance with anexception under 21 CFR 50.24 (FDA) or 45 CFR 46.101 or 45 CFR 46.116 (OHRP), depending on whether or not the research is subject to FDA regulation, and assuming that all required IRB determinations under these provisions can be made. 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.

In addition, advance notice of such planned emergency research protocols will be provided tothe Office for Human Research Protections pursuant to 45 CFR 46.101.
Also see:

- Informed Consent Requirements in Emergency Research [OHRP]
- Exception from Informed Consent for Studies Conducted in Emergency Settings [FDA]

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.

See the "Charge to IRB Members" by the Chief Scientific Officer (CSO).

Section 13 - Communication Among IRBs in Multi-SiteResearch

13.1 Communication among IRBs in Multi-Site Research

The IRB is responsible for the review of all Geisinger research that involves human research participants, whether the research is conducted at Geisinger, a Geisinger affiliate institution or another site outside of Geisinger if Geisinger staff are involved in the conduct of the research.

When Geisinger is conducting research at an external site and is not the coordinating site or lead investigator, and that site is engaged in research, the IRB requires contact information for the coordinating/lead site, whether the site has an IRB, and if so, confirmation of the IRB's permission to conduct the research.

Geisinger IRB relies on the IRBs of other sites and agrees to have other sites rely on Geisinger IRB. When the Single IRB (sIRB) process is used, an agreement (e.g., IRB Authorization Agreement (IAA), Reliance Agreement) is signed by the institutional officials of both site(s).

Geisinger Serving as Participating Institution

Geisinger PIs must follow all reporting requirements described in the agreement between Geisinger and the Reviewing IRB. When Geisinger is a participating institution (sending data or tissue samples out of Geisinger) the Geisinger PI must submit data in a timely manner to the coordinating institution, report Unanticipated Problems and other reportable events in a timely manner to the coordinating institution and the Geisinger IRB, and ensure that the PI's study team has the current approved version of the protocol and consent form.

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)

Relying on a Single IRB (sIRB)

Geisinger, through GIRB administrative review, may agree to rely on a single IRB (sIRB) for multisite studies to provide initial and ongoing regulatory reviews. The reliance terms are outlined in an IRB Authorization Agreement (IAA) or Reliance Agreement, e.g., Geisinger has signed on as a member of SMART IRB, which supports IRB reliance across the nation. SMART IRB is a platform designed to ease common challenges associated with initiating multisite research and to provide a roadmap for institutions to implement the NIH Single IRB Review policy (effective date: January 25, 2018). Freely available for institutions and investigators, SMART IRB is an integrated, comprehensive platform that allows flexibility in the size and scope of collaboration to enable IRB reliance for multisite studies across the nation, regardless of funding status.

The sIRB is responsible for reviews required by federal regulations at 45 CFR 46, and 21 CFR 50 and 56 (initial review, continuing review, modifications, reportable events). When Geisinger relies on a sIRB, GIRB still retains responsibility to ensure investigator compliance with the protocol, the sIRB's determinations, applicable federal and state regulations, and Geisinger policy. GIRB bears responsibility for the local conduct of these studies, e.g., managing noncompliance and

unanticipated problems, ensuring training, and study monitoring. In addition, local ancillary requirements, managing reliance agreements, and handling study specific issues that arise are GIRB's responsibility.

To request reliance on a sIRB, the PI is required to submit an *Application for Request for Ceding to an External IRB* within iRIS.

The IRB Role in the Central IRB (CIRB) for the National Cancer Institute

The CIRB is sponsored by the National Cancer Institute in consultation with the Department of Health and Human Services Office for Human Research Protections (OHRP). The Geisinger IRB functions as a liaison between the CIRB and the investigators, and as a resource to investigators when needed.

Geisinger IRB completes the Annual Institutional Worksheet which appraises the CIRBs of local context, includes required informed consent template language, applicable local and State regulations, and Geisinger policies. Investigators submit an Annual Investigator Worksheet for each investigator, and a Study- specific Worksheet for each study in which they wish toenroll participants directly to the CIRB. Each new study to CIRB is also entered into iRIS for an administrative review prior to the study team submission to CIRB. The CIRB is responsible for continuing review, review of subsequent modifications, non- compliance, and Unanticipated Problems. CIRB copies the IRB on notices when studies are initiated or closed. Investigators must submit all new study submissions, reports of local non-compliance, and Unanticipated Problems, KSP Amendments, and final reports within the iRIS electronic IRB system as well as directly to CIRB on forms designed for this purpose. See CIRB Submission and Review SOP.

The IRB Role with Health Care System Research Network (HCSRN)

Geisinger is member of the Health Care System Research Network (HCSRN). The HCSRN was established to reduce the burden on investigators from one HCSRN member who proposes to conduct research in multiple HCSRN member institutions. A reciprocal agreement has been signed by all the HCSRN sites to allow more efficient IRB review of protocols.

The Lead PI and Geisinger PI agree to use the HCSRN SOP's. The Lead PI prepares the IRB application used at his/her site. The application describes procedures at all involved sites.

Each submission where the Lead PI is not at Geisinger is submitted as a new study submission for Administrative Review of the submission to determine whether ceding would be appropriate. Investigators must also submit reports of local non-compliance, and Unanticipated Problems, KSP Amendments, and final reports within the iRIS electronic IRB system as well as directly to the HCSRN Lead PI on forms designed for this purpose.

The IRB Role with Western IRB(WIRB)

Geisinger contracted with Western IRB (WIRB) for review of all multi-center industry and adult clinical trials from 2006-2011. WIRB will retain the oversight of the industry study clinical trials until study closure.

Investigators with open studies at WIRB must follow all submission requirements for WIRB. The

submissions are not processed through the iRIS electronic IRB system for Geisinger IRB staffto conduct administrative review.

13.2 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)

Geisinger Serving as Coordinating Institution

When Geisinger is serving as the coordinating institution, the PI must describe the plans for communicating information relevant to the protection of participants among the participating sites and institutions as part of the study submission, including communications of adverse outcomes, prompt reporting (UP's and non-compliance), protocolamendment/modifications, and interim results.

When preparing study submissions, PIs must indicate if Geisinger is serving as the coordinating institution. The PI must list all other sites involved with the proposed research, the contact person at each site and contact information, such as phone number and email address. The PI must indicate if each participating site has an IRB and if that IRB has reviewedand approved the research.

When Geisinger is the coordinating institution receiving data or tissue samples from other sites the PI must submit the following documentation for each of the other participating sites along with the Study submission to the IRB before receiving any data or tissue samples from a site:

- IRB approval letter from each participating site that includes the type of review, the other institution's FWA information,
- Copies of appropriate data or tissue sharing agreements; and
- When appropriate, the consent forms from all participating sites.

The information will become part of Geisinger's iRIS study file for all internal and external reviews.

By submitting the study application form and supporting documents, the PI documents his/her acceptance of the responsibility of ensuring that all participating sites have obtained IRB approval prior to initiation of the research at that site. The participating sites must have written procedures that define the scope of studies subject to review by their IRB. The Geisinger IRB staff will review and confirm that each study submission for a Geisinger coordinating site project includes the appropriate documentation from all participating institutions.

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. A written agreement must be reached between the participating site and the Geisinger IRB which clearly outlines the review and approval procedures and roles and responsibilities of each site. This writtenagreement must be reviewed, approved and signed by the Institutional Officials from Geisinger and the Relying site.

For a prospective clinical trial, the consent forms used at all sites must indicate that data or samples are being sent to Geisinger. Data or tissue samples, even though they areanonymous, may not be received from an outside institution whose consent form prohibits data or tissue from going outside the institution.

There must be documentation of regular communication (e.g., teleconferences) withthe participating sites to update and inform all participating sites about progress of the study.

Reporting to the IRBs in Multi-Site Research

As the lead investigator at the coordinating institution, the PI is responsible for receiving data and reports from the outside sites in a timely manner and distributing them to the Geisinger IRB as required, (*see Section 3.9-Unanticipated Problems Involving Risks to Participants or Others, and Other Reportable Information*). Geisinger IRBs give the same considerations to such reports in multi-site research as they do to internal reports.

Identifying Material Changes in Multi-Site Protocols

The PI must report any material changes in the protocol that take place at any of theparticipating research sites. The IRB may require independent verification to ensure that no material changes have occurred in multi-site research or cooperative study protocols since the previous IRB review.

Section 14 - Principal Investigator Standards

14.1 Identification and Management of Conflict of Interest

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. (AAHRPP Element III.1.B)

Geisinger Policy 14.702 - Financial Conflicts of Interest in Research outlines policies regarding conflict of interest (COI) for research carried out at Geisinger, or elsewhere. Each investigator must report to Geisinger all his/her financial interests at least annually using Geisinger's Annual Conflict of Interest Questionnaire. Geisinger reserves the right to request additional information and supporting documentation as needed.

Disclosures of potential conflicts of interest are reviewed and resolved by the Research Conflict of Interest Committee (RCOIC). The IRB has the final authority to decide whether the potential conflict of interest and its management, if any, allows the research to be approved.

(See Sections 3.7-Conflicts of Interest (COI) and *6.3-IRB Composition and Membership)* and Policy 14.702 – Geisinger Policy on Financial Conflicts of Interest in Research.

14.2 Sound Study Design

Researchers employ sound study design in accordance with the standards of the discipline. (From AAHRPP Element III.1.C)

The significance of the research depends upon the validity of the results. It is unethical to put subjects at risk or to inconvenience them through participation in a study that may produce little or no reliable results. Geisinger policies, procedures, and education programs help Principal Investigators (PIs) and all Geisinger investigators conduct research studies in an ethical manner.

Regardless of the source of funding, it is the Principal Investigator's (PI) responsibility to judge the research design to be sound enough to meet its objectives before submitting the protocol for IRB review. The study submission documents address the various considerations for sound study design. When designing studies, the PI should consult the Guidance - Evaluating Sound Study Design and include all pertinent information in the study submission documents. The study submission also includes a description of the provisions for monitoring the data and reporting to the IRB and other entities (see Section 14.3 below).

In addition to following applicable federal, state, and local regulations, investigators follow ethical principles and standards appropriate for their discipline. In designing and conducting clinical trials, PIs follow Good Clinical Practice (GCP) guidelines defined by the Food and Drug Administration, and have the protection of participants' rights and welfare as their primary concern.

In developing, or in evaluating the adequacy of, a research design involving investigational drugs or biological products, the PI should refer to the FDA Guidance Documents representing the Agency's current thinking on good clinical practice (GCP) and the conduct of clinical trials, and

including selected guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH"), as published in the Federal Register on May 9, 1997.

The PI should also be familiar with the various types of control groups, their relative advantages and disadvantages, and the ethical issues associated with each control type, as outlined in the FDA guidance Choice of Control Group and Related Issues published May 2001. Although directly applicable to FDA-regulated trials involving investigational drugs or biological products, many of the principles can be applied to clinical trials in general.

14.3 Detection of Harm, Minimization of Risks and Mitigation of Potential Injuries through Study Design and During the Research

Researchers design studies in a manner that minimizes risks to participants. (From AAHRPP Element III.1.C)

Risks may affect physical, psychological, social, legal or economic well-being, including lossof privacy or breach of confidentiality. The PI must minimize risks at all times by using procedures that are consistent with sound research design and that do not expose participants tounnecessary risks, and whenever appropriate, by using procedures already being performed on the participants for diagnostic or treatment purposes.

During study submission to the IRB, the PI must:

- Describe the potential risks.
- Include, where possible, a scientific estimate of their frequency, severity, and reversibility. If statistical incidence of complication and the mortality rate of proposed procedures are known, this data should be included.
- Explain how risks will be minimized.
- Justify the level of risk.
- Describe adequate provisions for monitoring the data during the conduct of the research to minimize risk to participants (*see Section 9.2 – Minimize Risk).*
- Submit the study to Geisinger Scientific Review Committee (SRC) if investigator-initiated, without previous peer review and more than minimal risk.
- Documentation of successful SRC review outcome is uploaded with the submission to the IRB.

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.

For proposed changes to the research, including any change to mitigate potential harm to participants, the PI must submit an Amendment/Modification Form to the IRB describingany

resulting changes in the level of risk to participants, and explaining the risk level and potential benefits. If the federal support status of a study reviewed and granted an Exemption under Geisinger's flexible provisions (described above) 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 (2018 Revised Common Rule), 45 CFR 46.

During Continuing Review, the PI must indicate whether there has been an increase, no change, or a decrease in the level of risk of the study. If the risk assessment has changed, prior to submission of the Continuing Review the PI must submit a protocol Amendment/Modification to update the information in the Risks section of the protocol.

See also for additional information:

- Section 9 (measuring and minimizing risks to participants)
- Section 15.2 (Principal Investigator responsibilities in assessing and reporting events).

14.4 Recruitment

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

*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**)*

*Researchers and Research Staff recruit participants in a fair and equitable manner. (**AAHRPP Element III.1.E**)*

PIs must follow the Geisinger recruitment procedures outlined in Section 10.2.

The PI must provide all necessary information with the study submission to allow meaningful review by the IRB of the recruitment process. *(See Section 10.1 – Equitable Selection*).

In selecting a population from which to draw participants for a research protocol, the PI must consider whether the choice of population results in an equitable distribution of the burdens and benefits of research. The PI must provide appropriate justification in the study submission when recruiting participants among vulnerable populations such as pregnant women, economically and educationally disadvantaged, decisionally impaired, and homeless people. (45 CFR 46.111; 21 CFR 56.111(a) (3))

Employees and students

Per U.S. Department of Health and Human Services (HHS) regulations, employees and students are not listed as vulnerable populations; however, they may perceive that they are under some pressure from their superiors to agree to participate. PIs must provide a rationale for involvement of Geisinger employees or students by explaining:

- How they will be protected from coercion and undue influence, and
- What alternatives to participation exist?

Additionally, Guidance –Employees as Research Participants outlines the use of employees as

research participants.

Including Children as Participants

Children should be included in research, along with adults, unless there is a compelling rationale for their exclusion. See Chapter 9 -Risks to Vulnerable Populations – Children for more information about enrolling children in research.

Research that limits enrollment to children is generally not appropriate unless:

i. The condition or disease is limited to children, or
ii. The research seeks to obtain information on a test article or procedure that previously had been studied only in adults.

Appropriate Payment

Payments to research participants may not be of such an amount as to result in coercionor undue influence on the participant's decision to participate.

Payments may not be provided to participants on a schedule that results in coercion or undue influence on the participant's decision to continue participation. For example, payment may not be withheld as a condition of the participant completing the research. If the participant withdraws early, payment must be prorated to reflect the time and inconvenience of the participant's participation up to that point.

See Policy 14.313, Payments to Study Participants for uniform guidelines for the management and disbursement of payments to study participants.

Also see Guidance – Payment – Ethical Considerations.

14.5 Fair and Equitable Treatment of Research Participants

*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**)*

It is the policy of the Geisinger IRB to treat similarly situated research participants equally. This policy is informed by the following principles:

- Research, including research with human participants, is a good that should be facilitated
- Our patients and other members of the community should have opportunities to participate in research
- The burdens of participating in research should be cushioned, whenever possible
- In general, *similarly situated* participants should be treated equally

Questions about the appropriate application of this policy most frequently arise in the context of billing for study procedures and reimbursement to participants for research-related expenses. The purpose of this guidance is to help the Geisinger research community understand how this principle of equal treatment applies to a variety of situations that commonly occur in research.

Below are several examples of research practices that do and do not violate the policy of equal treatment. These examples are illustrative only and are not exhaustive of all situations in which the policy might apply. If you have questions about whether a research practice violates this policy, please contact the IRB Office.

Note: this policy is not meant to be an interpretation of various laws and regulations governing research billing, or of any other laws or regulations. Research in which Geisinger is engaged must comply with *both* this policy *and* all applicable laws and regulations. For questions about billing compliance and other compliance matters, please contact Research Compliance.

Examples of Research Practices That DO Violate the Policy

Example 1: Participants are reimbursed only if they travel a certain distance or more. For instance, traveling 50 miles or more is reimbursed; traveling fewer than 50 miles is not.

This practice is not permitted. Some participants may live far away from a study site while others live closer. It is permissible to reimburse participants according to the different distances they must travel (see Example 6, below). However, if some participants will be reimbursed for distances traveled, then all participants must be reimbursed for distances traveled.

Example 2: Reimbursement is provided only for participants who need assistance getting to study sites through a car service, taxi, or similar, but not for those who can drive themselves or who are driven free of charge by a friend, relative, community member, or similar.

This practice is not permitted. If participants who use taxis or other commercial drivers' services to travel to study sites are reimbursed for those fees, then other participants who drive themselves or get a ride free of charge from a friend, relative, community member, or similar must be reimbursed for mileage. Many participants in Geisinger research cannot drive themselves but rely on friends, relatives, or community members for free rides to study sites. It is not an appropriate response to the generosity of those friends, relatives, and community members to refuse to reimburse them for mileage when other participants are reimbursed for commercial driving service fees.

Example 3: Researchers conduct a day-long focus group in which professionals (e.g., physicians) are compensated $300 and laypersons are compensated $100.

This practice is not permitted. Participants who perform the same role in research must be compensated equally, even if their time is differently valued when they perform different tasks in their daily lives. If researchers need to offer higher amounts of money to professionals to compensate them for their time, then the same rate must be offered to laypersons performing the same research tasks.

Example 4: Researchers conduct two focus groups (or a study involving two arms, or two studies). The first focus group (or arm, or study) enrolls professionals (e.g., physicians), who are compensated $300. The second focus group (or arm, or study) enrolls laypersons, who are compensated $100.

This practice is not permitted for the same reasons given in Example 3, above. It is not permitted to pay professionals and laypersons different rates for performing the same study task (see Example 3), and this inequality is not eliminated simply by separating professionals and laypersons into two separate "arms" or by submitting two separate protocols in which participants within, but not across, scientifically unnecessary arms or studies are treated alike. Although there are of course many legitimate scientific reasons for creating multiple arms or protocols, they should not be created solely to avoid the policy of treating similarly situated participants. Although Examples 3 and 4 concern compensation for participation in focus groups, the same principle applies to other research practices, including but not limited to compensation or incentives for participating in other research tasks and reimbursement of research-related expenses.

Example 5: A study sponsor pays for a test only if the participant's insurance first denies it and an appeal also fails.

This practice is not permitted. Although it is permissible for a sponsor to pay only for those procedures that a participant would not have undergone outside of the study and to submit SOC procedures to insurance (see Examples 7 and 8), it is not permissible for the sponsor to first require that all study procedures, including those that are not SOC for the participant and therefore not expected to be covered, be submitted to insurance. Submitting claims to insurance that are expected to be denied creates needless work for the insurer, for research billing, and, most importantly, for research participants who must keep track of denials and ensure that they are then charged to research and not billed to participants.

Examples of Research Practices That DO NOT Violate the Policy

Example 6: All participants are reimbursed for mileage for travel to the study site, even though some will travel further than others and therefore receive different amounts of money in reimbursement.

This practice is allowed. All participants are treated alike in that they are reimbursed for the miles they actually traveled. Although some participants will receive greater amounts of money in reimbursement than others due to living further away from the study site, the reimbursement rate is applied to everyone similarly and fairly.

Example 7: A study investigates the effect of weight-loss surgery on individuals needing a total knee replacement. There are two arms: a control arm of patients who undergo a total knee replacement who are followed for two years, and a test arm of patients eligible for and interested in bariatric surgery, who first have that surgery and are then reevaluated for knee replacement after one year and followed for another two years. All surgeries are conducted as standard of care (SOC). In most cases, patients are recruited from an orthopedic clinic, where the screening visit and procedures are conducted as SOC. However, in other cases, patients are recruited from a weight loss clinic, in which case they are referred to orthopedics for a research screening visit to include x-ray. The sponsor (or the researcher, as appropriate) pays for non-SOC visits and x-rays only, requiring that SOC visits and x-rays be submitted to insurance or to the participant for payment.

This practice is permitted. If researchers or sponsors were required to pay for all procedures, even those that a participant would undergo had they declined to participate in the study, researchers and sponsors would have an incentive to exclude participants for whom study

procedures are non-SOC or to exclude Geisinger as a site entirely. These outcomes might affect the generalizability of the research in some cases, and it would deprive participants (in Example 7, patients who present to the weight loss clinic, or perhaps all Geisinger patients) of the opportunity to participate in research. Most importantly, participants who would receive a study-required procedure whether or not they enroll in the study and participants who would not undergo that procedure unless they enroll in the study are not similarly situated. Submitting claims to insurance can affect a patient's deductible or caps, but in this case, the cause is the participant's underlying condition and clinical need for the procedure, not the study.

Example 8: A study requires a blood draw and blood culture. Some — but not all — patients would already be undergoing a SOC blood draw and culture onto which the research draw could be piggybacked. The sponsor (or researcher) proposes to pay for only those draws that the patient would not undergo as SOC.

This practice is permitted. The phrase "standard of care" is frequently used in these contexts but, as in Example 7, *the key question in determining whether it is appropriate to charge some participants' procedures to research and other participants' procedures to their insurance (or to bill them directly) is whether the latter group of participants would have undergone that procedure even if they had not enrolled in the study.* If the answer is yes, then they and participants who undergo a procedure only because the study requires it are not similarly situated, and it is permissible to charge SOC procedures to patient-participants or their insurance and others to research.

Example 9: A study involves the collection of residual cord blood from new mothers/infants. In about 5-10% of cases, this turns out not to possible because, e.g., the cord blood is missed due to an urgent delivery or the blood spot testing by the state uses up the entire sample. In those cases, mothers are asked to collect a buccal swab from their infants at home. The sponsor pays the latter group of mothers a $25 gift card to compensate them for the effort of collecting and returning the sample and to provide an incentive for them to do so. Mothers from whom cord blood was successfully recovered from labor and delivery are not compensated.

This practice is permitted. All mothers who agree to participate in the study agree to have cord blood collected passively (as a byproduct of the labor and delivery process) and all have a (more or less) equal chance of that collection being successful. Collecting a buccal swab from a newborn is difficult, and mothers who perform that back-up specimen collection and those from whom the blood could be passively collected are not similarly situated.

14.6 Human Research Protection Resources

Researchers determine that the resources necessary to protect participants are present before conducting each research study. (AAHRPP Element III.1.D)

Principal Investigators (PIs) are required to indicate in the study submission to the IRB whether they will have access to adequate resources to carry out the research. Resources, includingspace, personnel, services and equipment required for conducting the proposed research properly and safely, must remain available as needed throughout the research.

PIs should continually monitor the resources allocated for their research and notify the IRB

if any change in the availability of resources may adversely impact the rights and welfare of participants.

When signing a study application, the Geisinger Principal Investigator must sign an assurance statement that certifies and assures the following:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research, including oversight and training of all investigators and study personnel to whom I have delegated research related responsibilities.
- I attest that I have an adequate number of qualified staff and facilities for the duration of the research study.
- Subject safety will be of paramount concern, and every effort will be made to protect subject rights and welfare.
- The research will be performed according to the IRB approved protocol, ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- My research team will: a) collect only information essential to the study and in accordance with the Minimum Necessary Standard, b) to the greatest extent possible, access to the information will be limited within the research team, and c) I will not reuse or disclose protected health information to any other person or entity, except as required by law, research oversight, or those uses outlined above.
- All members of the research team will be kept appraised of research goals and any modifications to the study plan.
- I will obtain IRB approval for this research study and any subsequent revisions prior to initiating the study or any change.
- I will obtain IRB continuing approval of this study prior to the expiration date of any approval period.
- I will report to the IRB any serious injuries and/or other unanticipated problems involving risk to participants.
- At the completion of the study I will complete a Final Report to the IRB.
- I am in compliance with the requirements set by Geisinger and qualify to serve as the principal investigator of this project or have acquired the appropriate approval per Policy 14.201.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities prior to leaving.

In addition to IRB approval of the protocol, human participant research (including recruitment and enrollment) which is sponsored cannot begin until a contract has been finalized, or a grant award activated.

14.7 Consent Process

Researchers employ consent processes and methods of documentation appropriate to the type of research and the study population, emphasizing the importance of comprehension and voluntary participation to foster informed decision-making by participants. (AAHRPP Element III.1.F)

Informed Consent is a Continuing Process

Informed consent is a continuing process where the investigator and research participant have an on-going dialogue about all aspects of a research study that might inform a participant's decision to take part in the study, and their decision to continue their involvement as a participant.
Although consent is given it may be withdrawn at any point. The informed consentprocess should be regarded as continuing throughout the duration of the research. The purpose of the consent process is to ensure knowledgeable decision-making and voluntaryparticipation.

The consent process generally includes:

- Bringing the research study to the notice of potential participants.
- Presentation and explanation by the investigator or delegate of the study and study activities to the participant or their legally authorized representative (LAR).
- Documentation of informed consent via a signed and dated consent document.
- Ongoing discussions between the investigator and the participant regarding continued participation in the study.
- Documentation of the consent process in the medical record.

The PI is expected to be familiar with:

- The consent process and consent form templates provided on the HRPP website. In addition, an informed consent checklist is available in the iRIS system HELP to assist investigators with all submission requirements.

The basic and possible additional consent requirements, and those specific to certain types of research activity (such as genetic testing, data and tissue repositories), are addressed in Section 12.1.

Consent requirements for research involving vulnerable and other special populations - including consent from a legally authorized representative (LAR) – are described in Section 12.2. This addresses adults with impaired decision-making capacity, children, pregnant women, fetusesand neonates, and Geisinger employees and students.

If the research involves extensive screening procedures, the PI may wish to develop an information sheet that explains the screening procedures in detail and provides a brief summary of the underlying research. In such circumstances, screening could begin after the individual reviewed and signed the consent document, which would be signed only if the individual satisfied the screening criteria and was actually enrolled in thestudy.

The Consent Document

The HRPP website provides consent form templates which address the required elements of informed consent. For research involving children, an assent template is alsoprovided.

To assist PIs in preparing consent documents comprehensible to lay persons (i.e., at approximately 6th to 8th grade level) a "Glossary of Lay Terms" is also available.

The IRB encourages and recommends the use of a full consent form, translated into the

participant's language whenever possible. In certain situations, the use of a 'short form consent process' may be permitted by the IRB, incorporating the use of a short form consent document translated into the participant's language.

If the PI proposes to use a consent document based on one already developed by the sponsor or a cooperative multi-site research group, the PI is responsible for reviewing the existing document to determine if it fairly and adequately describes the research aims, procedures, risks, and benefits. The explanation of risks in the consent document should be based upon information presented in such documents as the protocol, the investigator's brochure, any previous research reports, and, where applicable, the labeling for the drug ordevice.

See Section 12.1-Informed Consent and Assent for detailed information on consent documents, the long form, and the use of the short form consent process.

Requesting Waivers or Alteration of Consent Requirements

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:

6. The research involves no more than minimal risk to the subjects;
7. The research could not practicably be carried out without the requested waiver or alteration;
8. 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;
9. The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
10. Whenever appropriate, subjects will be provided with additional pertinentinformation after participation.

The PI may request that the IRB grant a:

- Waiver or alteration of the consent process – i.e., the requirements forobtaining informed consent, or
- Waiver of documentation of consent – i.e., the requirement to obtain a signature ona written consent document.

The requirements for these two options differ. Refer to *Section 12.5 – Waiver or Alteration of Informed Consent for additionaldetails*.

Obtaining Informed Consent

The PI is responsible for obtaining and documenting the informed consent of individuals who participate in research, unless IRB approves an alteration or waiver of the requirement to obtain and document informed consent.

Screening tests or procedures may not begin until after the participant has signed the consent form, unless the IRB has approved a waiver or alteration of consent.

It is ultimately the responsibility of the PI to ensure that those individuals are trained and carry out the tasks properly and in accordance with regulatory and IRB requirements. Unless the research is an interventional study including an investigational drug (IND) or device (IDE), the PI may delegate all or a portion of the informed consent process to others on the research team, such as co/sub-investigators, research coordinators, or other trained research staff. A U.S.-licensed physician who is a study team member is required to consent participants regarding the investigational drug (IND) or device (IDE) and its risks, benefits and alternatives. Before or after this discussion about the experimental product by the US-licensed physician, an IRB-approved, appropriately trained study team member may consent the research participant with respect to all other aspects of the research. The U.S.-licensed physician or other health care professional authorized to prescribe and administer the experimental product may administer the entire consenting process. The informed consent discussion must be documented in writing by each staff member who participated in the consent process (e.g., sign and date the informed consent form (ICF) or document in medical or research record). The research participant or legally authorized representative (LAR) must also sign and date the ICF.

The PI must follow the submitted and IRB approved consent process. IRB approved consent documents are available in the iRIS consent document file and must be used to consent potential study participants. The IRB approval date stamp will appear on the upper left-hand corner of the document.

No participants should be consented to be involved in research prior to the IRB approval date, and no participants should be involved in research if the study approval period has expired.

The PI or their delegate should plan to discuss the research study with potential participants at a time when they are not under duress and allow sufficient time and opportunity to askquestions to consider whether or not to participate in the research study.

In discussing research with potential participants, the PI or theirdelegate:

- May not describe items or procedures under investigation as if they were known to be safe and effective as a treatment for the potential participant's disease or condition, or as if they present a known advantage,
- May not understate the risks of the research, as there may be nocountervailing benefits to participants.

The PI or their delegate is responsible for providing the participant a copy of the signed informed consent document, and for maintaining the original form.

Consent Situations Requiring Prompt Reporting to the IRB

Situations where informed consent is not properly obtained or not documented, and no corresponding waiver or alteration of the consent process has been granted by the IRB, may constitute non-compliance. Such circumstances require reporting to the IRB. These include, but are not limited to:

- Involving an individual in research without first obtaining their informed consent and a signed informed consent document (unless the IRB has explicitly waivedthese requirements).
- Involving an individual in research using a consent form other than the current IRB-approved form.

- Situations where the PI believes informed consent documents have been lost, misplaced, or destroyed.

Also see the following:

- Section 12 on informed consent and assent.
- Section 15.2 for information on reporting to the IRB
- Section 3.8 - Non-Compliance with HRPP Requirements
- Guidance - Events and Information that Require Prompt Reporting to the IRB

14.8 Participants' Requests for Information and Complaints

*Researchers and Research Staff have a process to address participants' concerns, complaints, or requests for information. (**AAHRPP Element III.1.G**)*

Requests for Information

The PI and members of the research staff are required to respond promptly and adequately toall requests for information received from participants, prospective participants and/or their family members or designated representatives. In addition to providing information and answering questions that arise as part of the informed consent process, the PI must inform the participant that he/she is available to answer any questions that arise about the research in the future. The consent form must list the full name and contact information for the PI, and other research study staff as appropriate. The consent form must also inform participants how to reach the investigator or IRB if they have any questions about the research study or their rights as research subjects.

Participant Concerns or Complaints

Complaints from research participants or others can be directed to either the PI, IRB staff, or anonymously to the Compliance Hotline. Staff from the compliance hotline directly interact with the principal investigator and provide a summary report of the complaint to the Compliance Coordinating Committee. See Patient Calls – Complaints Flow Chart.

The PI is expected to investigate and respond promptly to participant concerns, complaints, or request for information about the research study, and to follow the proper procedure for addressing and reporting complaints to the IRB. A complaint is a formal or informal, written or oral, expression of dissatisfaction by the participant or the participant's representative.

Complaints are handled in accordance with the policies described in Sections 3.9 and 3.10. Also, see Guidance – Prompt Event Reporting to the IRB to determine whether immediate completion and submission of the Prompt Report Form is required or whether the event must be reported at the time of the next continuing review. See Process Flow – Patient Calls - Complaints.

At the time of Continuing Review, investigators are required to list all complaints received about the research in the past year, whether or not they were previously reported to the IRB.

Privacy issues

If the complaint involves Geisinger privacy practices, the institutional Privacy Officer should also be notified. All documentation relating to the complaint must be retained for at least six years from the date of creation.

Section 15 - Investigator Requirements

15.1 Qualifications and Training of the Principal Investigators (PIs) and Research Staff

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)

Training in the Protection of Human Subjects

Geisinger requires that PIs and other personnel involved in the design or conduct of a project, including projects deemed to be human subjects research under 45 CFR 46.101, complete training in the protection of human research participants prior to submission of research to the IRB for review and approval. The iRIS electronic IRB system includes an education validation tool which verifies completed education; therefore, expired education prohibits the submission rom proceeding to the IRB queue.

Geisinger employs the Collaborative Institutional Training Initiative (CITI) course as its human research training program. Required CITI training includes, Human Subject Research, Responsible Conduct of Research and Good Clinical Practices. Geisinger requires a refresher training course to be completed every three years.

Knowledge of Applicable Federal, State and Local Laws

The Institutional Review Board staff disseminates and make available to the Geisinger research community via the IRB website and education programs, the following resources to promote knowledge about applicable Federal, State and organization policies for human subjects research:

- HRPP Handbook and policies
- 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 for assistance

Where applicable, the Pennsylvania State laws have been included in the Geisinger HRPP Handbook. 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 or clinical investigation. Step-by-step guidance is available to the investigators on the Geisinger HRPP intranet: Geisinger Research Process Flow. This provides guidance necessary for submission and review through Geisinger IRB.

IRB staff is also 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" or "clinical investigation" 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, the investigator should contactthe HRPP staff or submit a Research Determination Worksheet (RDW). *(See 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 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: Additional training is provided for investigators who have additional responsibilities as the research sponsor
- Section 3.1 Agreement Includes Protection for Research Participants

15.2 Reporting to the IRB - Unanticipated Problems (Involving Risks to Participants or Others (UPs), 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

PIs are responsible for reporting Unanticipated Problems involving risks to participants or others and other reportable information to the IRB. For industry sponsored projects, PIs are responsible for maintaining communication with the sponsor and reporting suspected Unanticipated Problems and other reportable information to the IRB. For sponsor-investigator projects, the PI is solely responsible for reporting Unanticipated Problems and otherreportable information to the IRB. See additional reporting details in Section 3.9.

The Prompt Report Form is used to report to the IRB events or information, but PIs should consult with IRB staff before reporting such items.

Routine, periodic reports (e.g., Data Monitoring Committee 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 these reports to the IRB.

Assessment by Principal Investigator

The PI is responsible for the initial assessment of whether an event is an Unanticipated Problem or other reportable information.

PIs must assess each adverse event, whether received from a sponsor, monitoring entityor occurring on a sponsor-investigator project, and promptly report to the IRB, Unanticipated Problems and other reportable information according to the Guidance – Prompt Event Reporting to the IRB and Guidance – Unanticipated Problems vs Adverse Events.

In all cases, Unanticipated Problems that are deaths or life-threatening experiences related to the study (at Geisinger or when Geisinger is the coordinating institution in a multi-site study), must be reported within 5 working days from when the PI learns of the event.

Reporting Assessed Events and Information

For events required to be reported to the IRB, PIs should submit reports using the electronic iRIS Prompt Report Form. Adverse events that are deemed not to be Unanticipated Problems or other reportable information should be included in the narrative summary for the IRB during the Continuing Review.

The IRB will review and assess the events and information reported, and address them as described in the Section 3.9.

When Modifying the Protocol is Indicated

An event or new information might prompt an amendment/modification form – either initiated by the PI or specified by the IRB after reviewing a report. When an event or new information requires a modification to a previously approved protocol (e.g., new side-effect in the consent form or suspension of enrollment) an amendment/modification must be submitted for IRB review, and must be approved by the IRB prior to implementation of the proposed changes. The only exception to pre-approval is for modifications necessary to eliminate apparent immediate hazard to the research participants; in this case, the PI must submit an amendment/modification form to the IRB within 5 days following its implementation and include all specific details in the amendment.

Additional details are provided in the following:

- Section 3.9
- Guidance – Prompt Event Reporting to the IRB

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 recruitment or screening of the study.

It is the PI's responsibility to submit a written protocol to the IRB for review. At submission, the obligations of the PI with respect to oversight of their research protocols and researchstaff 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 tothe determinations and requirements of the IRB for the duration of the research.

The documents required for protocol submission are listed in Section 8.1.

A detailed discussion of the roles and responsibilities of IRBs is presented in Section 6. The general principles stated here apply to all human subject research.

Continuing Review Reporting

PIs must submit continuing review reports for FDA-regulated protocols to the IRB before the expiration date and in sufficient time to ensure the non-interruption of approval of studies.

Removal of Continuing Review Requirement

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 approved on or after January 21, 2019 and ongoing studies that are minimal risk and did not already transition will be 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, status of participant interaction and research activities and the criteria outlined below. Removal of the continuing review requirement will be communicated to the study PI in the Review Outcome Letter and documented in the study's electronic IRB record – Continuing Review and Expiration dates will be removed from the Study Outcome tab and Outcome letter.

If the IRB determines continuing review 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
- Research is eligible for expedite review in accordance with 45 CFR 46.110 with the following exceptions (per OHRP 2018 Requirements FAQs):
    - Where no subjects have been enrolled and no additional risks have been identified (expedited review category 8(b) - Studies that qualify for expedited category 8(b) 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.
    - Where (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 (expedited review category 9) – 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
    - Accessing follow-up care from procedures that participants would undergo as part of clinical care.
- Additional criteria:
    - FDA regulations do not apply to the study
    - Study sponsor does not require continuing review
    - No external institutions rely on GIRB for IRB review and ongoing oversight of their engagement in this study
    - 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 history of serious or continuing research non-compliance or pattern of non-serious non-compliance

Final Report

Upon completion of research initially approved via convened or expedite review, investigators are required to submit a final report to the IRB notifying the IRB of the completion of the research. Final reports are not required for research determined to be Exempt.

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.

Privacy and confidentiality are addressed in Section 11.

Privacy Rule (HIPAA)

When conducting research that involves the use and disclosure of protected health information (PHI), the PI must abide by the applicable HIPAA policy of the Geisinger and must submit an accounting of disclosures of PHI to Geisinger's System Privacy Office at the time of disclosure. *(See Section 11.3-HIPAA - Health Insurance Portability and Accountability Act Regulations)*

Delegation of Research Responsibilities

PIs may delegate research responsibility. However, PIs 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 well trained and competent.

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]. The FDA requirements are summarized in Guidance Special Considerations for the Oversight of Research Protocols in FDA-Regulated Drug or Device Studies.

In ***sponsor-investigator research***, the PI assumes all the responsibilities in overseeing the research normally assumed by sponsors in industry-sponsored projects.

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. The requirements applicable to a sponsor-investigator under this part include both those applicable to an

investigator and a sponsor.

Study Conduct

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)

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 tothe 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 trainedand supervised and that research duties are delegated to individuals qualified to perform the assigned tasks. Any non-compliance must be reported promptly to the IRB as required in Section 3.8.

The PI is also responsible for the timely and proper administration of the research project. Beyond the scientific and clinical conduct of the study, responsibilitiesinclude:

- Compliance with federal, state, local laws and Geisinger policies, including disclosure of any potential conflict ofinterest
- 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 atimely basis
- Submission of amendment/modification and continuing review applications ina timely manner
- Obtaining approval for changes prior toimplementation.

Oversight of Research Staff during Recruitment

The PI is responsible for ensuring recruitment activities, whether undertaken by research staff or the PI, use methods set forth in the study submission and protocol that was approved by the IRB. 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 knowledgeable about the research, while retaining ultimate responsibility over the conduct of the study.

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. See:

- Section 10.1 (Equitable Selection)
- Section 14.4 (Recruitment)
- Physician Attestation Form

Informed Consent

PIs are responsible for assuring the quality of the informed consent process and for makingsure that consent is obtained and documented before subject participation, unless waivers are granted by the IRB. For a detailed discussion of the informed consent process requirements and description of available templates and guidance, (*see Section 12 – Informed Consent and Assen*t)

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 participantsmust 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. It could be as simple as the protecting the data (how data isprotected, who has access, are you collecting the minimum necessary, etc.) in a retrospective record review or more complicated in clinical trials which would include some of the actual tests and procedures used for monitoring.

Monitoring may be conducted by the PI, or other means. (See Guidance – Data and Safety Monitoring) for examples of a Monitoring Entity (ME) In all studies, the PI has ultimate responsibility foridentifying potential risks and identifying adverse events occurring in the study population and reportingthe events to the sponsor and to the IRB as required in Section 3.10.

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 risksto 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

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 Element I.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 anequivalent 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., exculpatoryprovisions).

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

*In studies where Sponsors conduct research site monitoring visits or conduct monitoring activities remotely, Geisinger has a written agreement with the Sponsor that the Sponsor promptly reports to Geisinger findings that could affect the safety of participants or influence the conduct of the study. (**AAHRPP Element I.8.B**)*

Geisinger has included in their standard sponsored research contract templates, provisions that the sponsor will notify the Principal Investigator or the IRB of:

i. Non-compliance with the protocol or applicable laws, particularly those laws related to participants, that could impact the safety or welfare of the participants
ii. 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
iii. Unanticipated Problems in the protocol at Geisinger or any other site that could relate to risks to participating participants, and
iv. 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.

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

*When the Sponsor has the responsibility to conduct data and safety monitoring, Geisinger has a written agreement with the Sponsor that addresses provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to Geisinger. (**AAHRPP Element I.8.C**)*

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 in Guidance – Prompt Event Reporting to the IRB) are submitted according to the guidelines specified in this same guidance.

Section 18 - Knowledge Benefit and Participant's Interests

18.1 Publication of Research Results

*Before initiating research, the Organization has a written agreement with the Sponsor about plans for disseminating findings from the research and the roles that Researchers and Sponsors will play in the publication or disclosure of results. (**AAHRPP Element I.8.D**)*

Geisinger establishes the importance of disseminating research findings as one of itsmost 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 participant safety could be directly affected by study results after the study has ended, Geisinger has a written agreement with the Sponsor that the Researcher or Geisinger will be notified of the results to consider informing participants. (**AAHRPP Element I.8.E**)*

When the IRB learns of events that could affect participant welfare after a study has closed (e.g., a drug 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 whenthe study is not yet closed, but participants have completed participation, the PI must inform former participants when information is learned that could affect theirwelfare.

For sponsored research, Geisinger addresses communication with sponsors regarding the impact of research results on participant health and safety including a provision 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 doesnot use their standard template.

Section 19 - Addressing Concerns of Research Participants

19.1 Consent Form Requirements

*Geisinger has and follows written policies and procedures that establish a safe, confidential, and reliable channel for current, prospective, or past research participants or their designated representatives that permits them to discuss problems, concerns, and questions; obtain information; or offer input with an informed individual who is unaffiliated with the specific research protocol or plan. (**AAHRPP Element I.4.A.**)*

*Researchers and Research Staff have a process to address participants' concerns, complaints, or requests for information. (**AAHRPP Element III.1.G**)*

The IRB requires that all consent forms include information on how to contact the investigator(s) conducting the research study. Participants are instructed to call the investigators if they haveany questions about the research, about their rights as a research participant, or if they believe they have suffered a research-related injury. Each consent form must also include telephone numbers for the IRB (including a 24-hour number). 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. 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 conducts activities designed to enhance understanding of human research by participants, prospective participants, or their communities, when appropriate. These activities are evaluated on a regular basis for improvement. (**AAHRPP Element I.4.B.**)*

Geisinger's Research Website

The 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 webpagesdevotedtoresearch administration, core services, and resources (e.g., HRPP and Research Ethics andConsultation)
- Departments & Centers – provides an overview of research centers and institutes, as well as clinical departments and institutes conductingresearch
- 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 thestudy
- *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

Geisinger conducts activities designed to enhance understanding of human research by participants, prospective participants, or their communities, when appropriate. These activities are evaluated on a regular basis for improvement. ***(AAHRPP Element I.4.B.)***

Information about Geisinger's human research studies and opportunities for community member involvement as partners in research can be found in the following resources:

- Get Involved with Research at Geisinger
- Learn About Clinical Studies
- Become a Research Volunteer
- Becoming a Research Volunteer: It's Your Decision
- MyGeisinger – a secure, web-based tool – 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.
  - **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.
  - **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.
  - **Personal Research Options** – Provides patients or someone in their family information about a particular area of research. Patients can complete a form and staff will search the current research programs at Geisinger and try to match them with a research opportunity. Patients will receive a response within 2 working days.
  - **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.
  - **What's New in Research?** – Provides details about research at Geisinger.

20.3 Community Participation in Research

Geisinger promotes the involvement of community members, when appropriate, in the design and implementation of research and the dissemination of results. ***(AAHRPP Element I.4.C)***

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 195,000 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 eight members, including four 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:

- *Putting Patients at the Center of Kidney Care Transitions*
- *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 a 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

To support and facilitate engagement of our patient community in all aspects of the LHS, researchers are currently writing a letter of intent for a PCORI capacity building grant and the purpose, if funded, will be to develop a curriculum for prospective patient/community member participation in research – as study team members, as advisors and/or as overseers. Geisinger IRB also supports this goal through inclusion of patient representatives and members who have expertise in community participatory research.

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.

Appendices

Delegation of HRPP Authority Letter

(back to page)

February 19, 2015

David H. Ledbetter, Ph.D., FACMG
Executive Vice President
Chief Scientific Officer
Institutional Official
100 N. Academy Avenue, MC 22-01
Danville, PA 17822

RE: Delegation of Authority for the Human Research Protection Program (HRPP)

I hereby delegate authority and responsibility to the Executive Vice President/Chief Scientific Officer (EVP/CSO) and Institutional Official (IO) to establish, maintain and oversee the Human Research Protection Program (HRPP) at Geisinger Health System (GHS). "Geisinger Health System", "GHS" or the terms "System", or "Geisinger" shall refer to the entire Health Care System comprised of t h e Geisinger Health System Foundation as parent and all subsidiary corporate entities. HRPP covers not only Geisinger Medical Center but all Geisinger clinics and hospitals as well as affiliates identified on Geisinger's Federalwide Assurance FWA00000063.

This delegation includes but is not limited to:

1. Oversight of the Office of Research Compliance (ORC), the Institutional Review Board (IRB) and its members, including the appointment of the Chairs and members.
2. Oversight of the HRPP and related research policies and procedures on behalf of Geisinger.
3. Appointment of panels or advisory groups as needed for Human Research Protection Program (HRPP) oversight.
4. Maintaining open channels of communication between all the components of the HRPP.
5. Oversight of research investigators and staff, administration, and research management.
6. Ensuring the independence of the IRB, including the authority to act without undue influence.
7. Periodic reviews of the HRPP by ensuring 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,

Glenn D. Steele, Jr., M.D., Ph.D.
President and Chief Executive Officer

CC: Dorothy Sellers, Director, Office of Research Compliance (ORC)

Charge to the IRB Members

BY GEISINGER'S EXECUTIVE VICEPRESIDENT AND CHIEF SCIENTIFIC OFFICER (back to page)

General Charge

The 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 and its affiliates, (the acronym "GHS" or the terms "System", "Geisinger", or "Geisinger Health" shall refer to the entire Health Care System comprised of theGeisinger Health as parent and all subsidiary corporate entities) including all Geisinger Hospitals and clinics. Some functions are described in this General Charge.

A full description of their duties and responsibilities is contained in the HRPP Handbook.

The primary function of the IRB is the prospective and continuing review and approval of all Geisinger human subject research. The objective of the IRB is to ensure that the rights and welfare of research participants are adequately protected and that all activities involving human subjects are in compliance withapplicable Geisinger policies and external regulations.

The IRB is assigned the authority and responsibility for reviewing all protocols involving human subjects (as defined below and in Section 1 of the HRPP Handbook) that are conducted at Geisinger facilities or by Geisinger physicians, staff, students or visiting scientists at any location. This includes the authority to observe the informed consent 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, but not less than once per year, regardless of the source of funding. 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, as outlined in Section 3 of the HRPP Handbook. The IRB has the authority to take action based on 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 Executive Vice President and Chief Scientific Officer (EVP and CSO), 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, the HRPP staff will formulate draft policies and procedures for approval by the EVP and CSO.

Definitions

Department of Health and Human Services (DHHS) Regulations (45 CFR 46):

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

1. Data through intervention or interaction with the individual, or
2. Identifiable private information.

Research: A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

Food and Drug Administration (FDA) Regulations (21 CFR 50 & 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.

IRB Guidelines

The HRPP Handbook is used to aid the IRB with their responsibilities as summarized below:

1. Research projects shall be reviewed in such a manner as to provide for the protection of the participant against undue or unnecessary invasion of privacy, disrespect for human dignity, and physical, psychological or social harm. In most cases, this will involve review and approval of a clearly-worded consent form to assure that participants are fully informed of the risks inherent in participation and of the benefits which might be reasonably expected.
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; 21 CFR 56.107 (e): "No IRB may have a member participate in the IRB's initial or continuing reviewof any project in which the member has a conflicting interest except to provide information requested by the IRB." The member must leave the meeting room prior to voting on the study outcome. The standards for determining if a conflict exists and the steps to take if it does are set out in Section 6 of the HRPPHandbook.

3. All research protocols involving the use of 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 a protocol may be granted for no more than one year (365 days); however, appropriate to the degree of risk. Except for life-threatening emergencies and protocols qualifying for expedited or exempt review, all protocols must be approved at a convened meeting of a quorum (i.e., a majority of the voting members-one more than 50%, including at least one member whose primary concerns are in non-scientific areas and one member whose primary concerns are scientific areas) with the affirmative vote of a majority of those present. The IRB review process and requirements are discussed in Section 7 of the HRPP Handbook.

Appeals

In cases of dispute with respect to procedures or decisions of the IRB, appeals may be made to the IRB Chairs or Director, IRB Operations and HRPP. The details and process for such an appeal are set forth in Section 6 of the HRPP Handbook. As this document makes clear, neither the EVP and CSO, nor Chief Executive Officer (CEO), 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 IRB to reverse a decision (as further provided in Section 3 of the HRPPHandbook).

Membership

The IRB members are appointed by the IRB Chairs with input from the Director, IRB Operations and HRPP. The membership includes: at least one member whose primary concerns are non-scientific, at least one member from the local community and who is not otherwise affiliated with Geisinger, at least one member whose primary concerns are scientific, and others who may be invited to serve when their expertise is required, such as, pediatrics, pregnant women, genetics, nursing, etc.

Non-voting ex officio members include but are not limited to representatives of the: Bioethics. Membership is explained in Section 6 of the HRPP Handbook.

The term of membership is generally three years and is renewable beginning July 1 through June 30th.

Reporting Obligations

The IRB reports to the EVP and CSO, who is the institutional official (IO) responsible for assuring compliance with policies and external regulations on the use of human subjects in research and providing oversight for the HRPP.

Meetings

The IRB meetings are held the first and third Thursday of each month at 2:30 pm.

Staff Support

The EVP and CSO shall provide the necessary staffing and administrative assistance for the IRB through the Chief Administrative Officer.

Sample PI Status Request Letter - ***[this is a sample only; please fashion letters to meet specific instances]***

To request PI status on a proposal to an external agency, internal funding or an IRB, IBC, IACUC protocol or Radiation License

Memorandum

To: Terri Bickert DNP RN NEA-BC, Vice President, Nursing
System Education, Research & Magnet
From: [chair of center/department]
Re: Request for PI Status for [individual]

Example #1: External Source of Funding: Joan Doe wishes to apply for support from the American Council of Cancer Researchers under its [name of program]. The title of the proposal is "xxxxxxxxxxx".

Example #2: PI on an IRB protocol: Joan Doe wishes to serve as PI on a human research study, entitled "xxxxxxxxxx". This project will [xxxxxxxxx].

Ms. Doe is currently [a – add title and describe role]. This position does not normally include the privilege of serving as PI. I write to ask that she be allowed to serve as PI on this application/protocol/period of time/set of projects for the following reasons.

Example only – Please tailor to specific situation: The ACCR's Young Investigator Award aims to develop outstanding research scientists in basic biology in areas relevant to leukemia. In conjunction with Dr. Adam West, Dr. Doe has pursued research in AML. She has developed a research plan to explore [research area], an area of direct interest to the ACCR. Through its Young Investigator Program, the ACCR can provide salary support and some research funds to pursue this worthwhile/important research area.

The ACCR requires that the candidate serve as PI on applications for the Young Investigator Award. This award is appropriate for Joan Doe's training, abilities and goals. Dr. Doe has already demonstrated the necessary expertise to pursue this project and the independence required to serve as PI on this project.

On behalf of the Department of Hematology and Adam West, I can confirm that the necessary release of time and research resources will be available to ensure that the success of the proposed program. In addition, the department will assume responsibility for the fiscal, administrative and programmatic oversight of this project and will guide Joan Doe in her responsibilities as PI. Adam West will serve as primary mentor to Joan Doe, and will be assisted in this process by Ana Wolff as necessary.

For all the foregoing reasons, I believe it is appropriate that Joan Doe serve as PI on the proposed proposal. Attached please find Joan Doe's CV and an abstract of the project.

Thank you for your consideration of this request.

Attachment:
Joan Doe's CV
Abstract of the project

14.201- Principal Investigator or Program Director Status

(back to page)

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, HCSRN, 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

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09.105 - Research Permitted Use and Disclosure of PHI for Research

(back to page) 121 (back to page) 145

PURPOSE:

The purpose of these procedures is to describe the process for release of a Limited Data Set (as later defined) by workforce members of the above referenced entities (the "Covered Entities") for research purposes through a Data Use Agreement.

All workforce members looking to collect Data and send externally to an Outside Entity (as later defined). As defined by the Department of Health and Human Services ("DOH" or "HSS"), Workforce members include employees, volunteers, trainees, and may also include other persons whose conduct is under the direct control of the entity (whether or not they are paid by the entity).

POLICY:

A. This Policy is written to determine when Data (as defined below) may be disclosed to an Outside Entity. Data may include any of the following types of datasets (all defined herein)

- Disclosure of Protected Health Information (PHI)
- Limited Data Set (LDS)
- De-Identified Data

1. **Disclosure of Protected Health Information (PHI)**

   HIPAA Authorization: The IRB/Privacy Board may approve the use and disclosure of PHI according to the terms of a completed and signed Research Consent/Authorization form. Permissible uses and disclosures are limited to those described in the consent/authorization form. The IRB may also approve the use and disclosure of PHI without patient authorization if the request meets certain criteria. A waiver of patient authorization must be obtained from the IRB.

2. **Disclosure of a Limited Dataset:**

   Geisinger researchers may disclose a Limited Dataset only if the Covered Entities and the Outside Entity have entered into a Data Use Agreement (DUA) stating that such outside entity will only use or disclose the Limited Data Set for limited purposes.

3. **Disclosure of De-Identified Data:**

   The IRB may determine that the data is being recorded and will be used in such a way that it is de-identified (as defined below) and all elements of PHI will have been removed from the dataset. For datasets being disclosed to an Outside Entity, IRB review to determine if the dataset is de- identified is required. If the dataset being disclosed is de-identified, a DUA or other applicable Agreement is required.

Note: Except for Limited Datasets and/or de-identified datasets, disclosure of PHI pursuant to a waiver must be tracked, and reported in the Accounting for Disclosure database, whereas disclosures of PHI pursuant to a HIPAA authorization need not be tracked.

B. No PHI, LDS or De-Identified Dataset may be disclosed unless and until one of the following agreements is in place:

   a. **Data Use Agreement (DUA) or Agreement for Disclosure of PHI**: Requests for uses and disclosures of PHI for research purposes should be made to Research Contracts;

   b. **Clinical trial or sponsored research agreement or sub-award**: A project Agreement in place that restricts the use and further disclosure of the dataset by the Outside Entity.

C. Geisinger Researchers may disclose Data only if the Covered Entities and the Outside Entity have entered into a DUA or other applicable Agreement stating that the Outside Entity will only Use or disclose the Data for limited purposes, which are set forth in the DUA or other applicable Agreement. Research Administration shall be the department responsible for the negotiation and execution of the DUA or other applicable Agreement for which a Researcher has expressed interested in obtaining. A DUA or other applicable Agreement shall be executed for the purpose of conducting a Research project.

   a. The Data will not be disclosed to any entity outside the Agreement without prior authorization from GHS or otherwise as required by applicable law.

   b. The Researcher and Outside Entity will safeguard the data to prevent use or disclosure of the information other than as provided by the Agreement

   c. The Researcher will maintain and make available upon request an Accounting of Disclosures for all disclosures under the Agreement

   d. The Researcher and Outside Entity will promptly report to the Geisinger IRB any use or disclosure of the information not provided for in the Agreement

   e. The agreement should require any of the Outside Entity's subcontractors or agents that receive or have access to the Data to agree to the same restrictions and conditions onthe use and/or disclosure of the Data that apply to the Outside Entity under this Agreement; and

   f. The Outside Entity may not use the information in the Data to identify or contact the individuals who are data subjects

DEFINITIONS:

Accounting of Disclosures: is a required recording by a covered entity of what PHI was disclosed, to whom it was disclosed, and the date and purpose of the disclosure. When multiple disclosures of PHI are made to the same person or entity for a single purpose, the accounting for such disclosures may consist of the information described above for the first disclosure, plus the number or frequency of disclosures, and the date of the last disclosure during the time period covered by the request. [See 45 CFR 164.528.]

Covered Entity: is a health plan, health care clearinghouse, and any health care provider who transmits health information in electronic form in connection with transactions for which the Secretary of HHS has adopted standards under HIPAA (the "covered entities") The Privacy Rule, as well as all the Administrative Simplification rules, apply to all Covered Entities. [See 45 CFR 160.103.]

Data: Protected Health Information, a Limited Dataset or a De-identified dataset as defined herein.

Data Use Agreement ("DUA"): is a satisfactory assurance between the Covered Entity and an Outside Entity using a Limited Data Set that the data will only be used for specific uses and disclosures. § 164.514(a) and (b) and cannot have links for re-identification. De- identified data is considered not to be individually identifiable health information.

De-Identified Data: is a satisfactory assurance between the Covered Entity and an Outside Entity using a Limited Data Set that the data will only be used for specific uses and disclosures. § 164.514(a) and (b) and cannot have links for re-identification. De- identified data is considered not to be individually identifiable health information.

Limited Data Set: is protected health information from which certain specified direct identifiers of individuals and their relatives, household members, and employers have been removed. A LDS may be used and disclosed for research, health care operations, and public health purposes, provided the recipient enters into a DUA promising specified safeguards for the protected health information within the LDS. For a list of PHI allowable within a LDS, please see 45 CFR 164.514(e).

Outside Entity:is an individual, company, institution and/or federal agency that is receiving the Data from Geisinger (Note: This includes Geisinger Health Plan)

Protected Health Information (PHI): is defined as individually identifiable health information that is transmitted or maintained in any form or medium (electronic, oral, or paper), by a Covered Entity or Business Associate (as defined by HIPAA Regulations). [See 45 CFR160.103 as amended from time to time.]

Research: means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. [See 45 CFR 164.501.]

Researcher: must be the Principal Investigator (PI) and is someone who is professionally engaged in research. He/she must be Geisinger-employed permanent professional staff with advanced degrees (MD, DO, or PhD) or has been provided with approval to be a PI or Program Director (PD).

Use: means, with respect to individually identifiable health information, the sharing, employment, application, utilization, examination, or analysis of such information within an entity holding such information [See 45 CFR 160.103.]

11.609 - Investigational Drugs

(page to page)

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 System (GHS).

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 aremade.
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 GHS IRB and the Investigational Drug Pharmacy.

DEFINITIONS:

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.

Emergency Use of an Investigational Drug: The use of an Investigational Drug outside of a GHS 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 GHS IRB approval.

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.

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.

Institutional Review Board: Any specifically constituted review body that has been formally designated to review and monitor biomedical research involving human subjects.

PROCEDURE:

A. 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 and FDA 1572 (when applicable) on file.

1. For any GHS IRB-approved INPATIENT study: Any GHS 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.
2. 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.
    v. All medications leaving the clinic with subjects will be labeled with the CLINIC name, INVESTIGATOR name, and 24-hour PHONE NUMBER, and CLEAR directions.

Note: Any clinic handling its own medication as part of a GHS IRB-approved protocol shall be audited internally by the IDS Pharmacy at least annually. The results of the audit will be reported to the IRB.

B. Inpatient and Outpatient use of Investigational drugs for GHS IRB-Approved protocols: dispensed by the GHS Investigational Drug Pharmacy:

1. 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.
2. 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).
3. 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.

4. 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.
5. 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.

C. Inpatient and Outpatient Use of Investigational Drugs from GHS IRB-Approved outpatient protocols that are not dispensed by the GHS IDS Pharmacy:

1. 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.

2. 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.

3. Inpatient use of Investigational Drugs from GHS IRB-Approved outpatient protocols not dispensed by the GHS IDS Pharmacy will be handled according to the GHS policy 11.228 (Medication Management: Home Medication Management) and will not be dispensed from the GHS IDS Pharmacy.

D. Inpatient use of Investigational Drugs dispensed from other institutions:

1. Investigational drugs from other institutions will be handled according to the GHS 11.228 (Medication Management: Home Medication Management) and will not be dispensed from the GHS IDS Pharmacy.

2. The GHS 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.

3. The GHS attending physician or designee will obtain a summary or copy of the approved protocol and place it in the patient's medical record.

4. The GHS attending physician or designee will obtain a summary or copy of the signed informed consent and place it in the patient's medical record.

5. The GHS 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.

E. Emergency Use of an Investigational Drug outside of an IRB-approved protocol:

1. 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.

2. The PI will obtain informed consent from the patient or his/her surrogate decision maker according to IRB requirements

3. The PI will notify the IRB of the use of the investigational drug according to the IRB requirements.

4. The IDS Pharmacy will provide the available drug information to the GHS staff treating and monitoring the patient.

14.313 - Payments to Study Participants

(back to page) 116 (back to page) 153

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 a IRS 1099 form if they equal or exceed the current IRS reporting threshold.

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 inventorylog.
- 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.
- All gift cards must be purchased through Accounts Payable. A Request for Payment is processed and submitted to Accounts Payable.
- The use of generic gift cards is encouraged. Imprinted holiday, animal, and other themes are not allowed.
- 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 thestudy.
- 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 or gas stations), these cards must be donated to a Geisinger charity event. The cost for these cards must be absorbed by the homeunit.
- 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.

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 giftcard.
  • 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.

DEFINITIONS:

Form 1099: official form used by the Internal Revenue Service used to report various types of income other than wages.

14.107- Human Research Using Radiation Sources

(back to page)

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.

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 a 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 PA 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 beused
    - 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 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 mean 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 Subcommitee, consisting of the RSC Chair, RSO, the general Radiology representative on the RSCs, and one provider from each RSC, 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.

14.707 – Research Education and Training Policy

Back to page

PURPOSE:

The purpose of this policy is outline the required research educational training requirements required by Investigators, research staff, and compliance committee members, such as Institutional Review Board (IRB) and Animal Care and Use (ACUC) that are necessary to achieve a high level of professional and ethical behavior in the conduct of research at Geisinger[1]

[1]Throughout this document the terms "Geisinger", “Geisinger Health System” and “Health System” shall refer to any legal entity involved with research activities or the provision of health care services within the entire health care system comprised of the Geisinger Health System Foundation (the "Foundation") as parent and all subsidiary corporate entities comprising the Health Care System.

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.

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 requirements will vary depending upon the type of research, such as, animal vs. human subject research. Training must be completed prior to:

* Obtaining access to iRIS (Geisinger’s electronic IRB system)
* Submitting a new study application or amendment to the IRB or ACUC
* Adding new investigators and research staff to a research study or grant application
* Submission of a grant application
* Processing a grant award notice
* Execution of a sponsored research contract
* Committee member review of study submissions

Two training options have been developed through the Collaborative Institutional Training Initiative (CITI) – one for animal researchers and staff and the other for human subjects researchers and staff. Both training options include Good Clinical Practice (GCP) and Responsible Conduct of Research (RCR) training. All researchers and staff must first complete a basic training course prior to completion of the refresher course. The available training modules include:

* Basic – Animal Researchers & Staff - Researchers and research staff conducting **only** animal research – GCP and RCR courses must also be completed.

- Refresher – Animal Researchers & Staff – Required every three years thereafter.

* Basic – Human Subject & Data Only Researchers & Staff, IRB Members & Staff – Researchers and staff conducting human subjects research - GCP and RCR courses must also be completed.
  - Refresher – Human Subject & Data Only Researchers & Staff, IRB Members & Staff – Required every three years thereafter.

Additional didactic RCR training courses are required for all Post-Docs 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.**

External researchers or staff conducting research at Geisinger

External researchers or staff conducting human subject research at Geisinger must complete Human Subject Research (HSR) training. Training from their "home" institution is accepted unless the external researchers or staff have a dual appointment with Geisinger. If so, the staff must comply with Geisinger's training requirements.

The external staff must send an e-mail to the Office of Research Compliance (ORC) at orc@geisinger.edu with a copy of the training certificate attached. The certificate should include the title of the course, completion and expiration date. ORC staff will forward the training certificates to IRB staff to update training in iRIS and upload into the appropriate iRIS user account.

External researchers and research staff training exception

If Geisinger researchers and staff are conducting research under a sub-award with another institution and the external site is using Geisinger Health System (GHS) data, the external researchers or staff **MUST** comply with their home site training requirements and are not required to follow Geisinger's training requirements.
The following is a description of the training course contents:

* **Animal Care and Use (ACU) Training** – Includes general principles of ethical care and use of animals in research, training, and testing, as well as focusing on the care and use of particular animals. The training addresses the needs of the entire research team: investigators, students, technicians, and administrators. Additional information is provided to help investigators learn how to work more productively with the Institutional Animal Care and Use Committee (IACUC), and for members of the IACUC itself.

* **Conflict of Interest (COI) Training** – Includes details on the revised Public Health Service (PHS) regulations associated with financial conflicts of interest and an investigator's responsibilities relating to the disclosure of "Significant Financial Interests" by describing different types of conflicts of interest, conflict of commitment, and reasons why they can be problematic.

* **Good Clinical Practice (GCP) Training** – 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 Research (HSR) Training** – 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.
* **Responsible Conduct of Research (RCR) Training** – The practice of scientific investigation with integrity. It involves the awareness and application of established professional norms and ethical principles in the performance of all activities related to scientific research. (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 either the IRB or ACU or be included on a research study, grant, or contract submission.

DEFINITIONS:

1. ***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 (which may include, for example, collaborators and consultants), regardless of Research funding source.
2. ***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).

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-10-019) http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-10-019.html

Geisinger HRPP - Requirements for Department of Defense (DoD) Human Subjects Research

PURPOSE:

Research supported by the Department of Defense (DoD) involving collaboration with DoD or involving DoD facilities or personnel (military or civilian), is subject to additional requirements including special protections for research participants, as well as additional review and reporting requirements for investigators and IRBs. Investigators should review these requirements when planning a DoD-supported research project as they may add a significant amount of time to the human subjects review and approval process throughout the research.

The focus of this policy is on requirements outlined in DoD Instruction 3216.02, *Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research* (October 15, 2018) and in Navy guidance SECNAV Instruction 3900.39D, *Human Research Protection Program* (November 6, 2006). For a checklist of investigator responsibilities related to DoD sponsored research, see the DoD PI Checklist.

Each DoD Component (e.g., Army, Navy, Air Force) may have additional requirements beyond those included in this guidance document. Principal investigators are advised to check with their sponsoring Component program manager about any additional requirements.

PERSONS AFFECTED:

Institutional Review Board, Office of Sponsored Programs, Researchers and Study Personnel

DEFINITIONS:

Experimental Subject:
Research involving an **Experimental subject**: An activity, for research purposes, where there is an intervention or interaction with a human subject for the primary purpose of obtaining the effect of the intervention of interaction (32 CFR 219.102(f)).

Minimal Risk:
The DoD Instruction cautions that the Common Rule definition of **minimal risk** that includes the phrase “ordinarily encountered in daily life or during the performance of routine physical or psychological tests” must not be interpreted to include the inherent risks that certain individuals face in their everyday lives, such as a soldier in a combat zone or an individual who has a particular medical condition.

POLICY:

When conducting DoD research, FDA (21CFR50 & 56) and DHHS (45CFR46) human subjects research regulations apply, however when Human Research is conducted or supported by the Department of Defense (DOD), this Organization commits to also apply the Department of Defense (DOD) Directive 3216.02, which includes the requirement to apply 45 CFR §46 Subparts B, C, and D. This Organization will comply with the terms of the DFARS clause or comparable language used in the agreement with the Department of Defense (DOD) Component supporting the research involving human subjects.

1. **When is Human Research Subject to DoD Special Requirements?**

Human research must comply with DoD requirements when:

- The research is funded by a DoD Component (Attachment A), including cases where Geisinger is the recipient of a subaward from the direct recipient of DoD funds, or
- The research involves cooperation, collaboration or other type of agreement with a DoD Component, or
- The research uses property, facilities, or assets of a DoD Component, or
- The subject population will intentionally include personnel (military and/or civilian) from a DoD Component. (DoD requirements do not apply when DoD personnel incidentally participate as research subjects where they are not the intended research population or where the project is not DoD-supported).

2. **Required DoD Human Research Protections Office (HRPO) Administrative Review**

Upon completion of Geisinger IRB review and approval, including determination of exempt or not IRB- regulated status, the HRPO for the sponsoring component must perform an administrative review of the research before activities with human subjects may begin. The review involves confirmation that the Institution and the proposed research are in compliance with DoD requirements for the protection of human subjects. While the HRPO review is not an IRB review, the HRPO may require changes to the research prior to the start of the research. The Principal Investigator is responsible for submitting the information required by the sponsoring Component.

3. **Special Requirements for IRB Review of DoD Research**

3.1 Training Requirements

DoD requires that all individuals involved in the "design, conduct, or approval of human subjects research" complete human subjects research training. Geisinger's CITI human subjects protections training, renewable every three years, meets the training requirements for many DoD Components. Investigators are responsible for ensuring that all study team members engaged in the conduct of human subjects research complete CITI. The DoD Component may evaluate the institution's training program to ensure that personnel are qualified to perform the research, based upon the complexity and risk of the research.

3.2 Scientific Review

Research involving components of the Army or Navy (including Marine Corps) may require documentation of scientific review prior to IRB review of new applications and substantive amendments.

The scientific review may be the review provided by the funding agency (including DoD), or by Geisinger Scientific Review Committee. In some cases, the evaluation of scientific merit that is conducted by the IRB as part of its review is sufficient. The IRB or DoD program manager can assist with the determination of the appropriate review mechanism.

If required, documentation of the scientific review must be provided to the IRB at the time the IRB application is submitted and for substantive amendments. Scientific review must demonstrate that the research uses procedures consistent with sound research design and is likely to yield the expected results and should include the assessment of the following elements:

- Significance of the research question;
- Scientific approach;
- Research team qualifications; and
- Facilities and resources available.

The name and qualification of the reviewer(s) should be included as part of the review.

3.3 DoD Approval of Surveys/Interviews

Research involving surveys or interviews with DoD personnel (military or civilian) or their families may require DoD approval. The DoD Component program manager can confirm any additional review requirements and the timing of the review (before or after IRB review). Documentation of this review must be provided to the IRB.

3.4 Collaboration with other Institutions

Collaborating institutions in multi-site research must hold a federalwide assurance or individual investigators must be covered by an Individual Investigator Agreement with Geisinger. Study teams must provide the following:

- Documentation of IRB approval or IRB Authorization Agreement for engaged collaborators; and
- A statement of compliance with special DOD requirements.

4. Unique Human Subject Protections Required for DoD-related Research

4.1Prohibited Research

- Research with detainees (prisoners of war), except research with investigational new drugs or devices where such treatment would also be offered to US military service members at the same location and with the same medical condition consistent with established medical practice.
  DoD Instruction 2310.01E defines a **detainee** as: "Any individual captured by, or transferred to the custody or control of, DoD personnel pursuant to the law of war. This does not include persons being held solely for law enforcement purposes, except where the United States is the occupying power. Detainees who are U.S. citizens or U.S. resident aliens will continue to enjoy all applicable rights and privileges under U.S. law and DoD regulations."

- Classified human subjects research: Geisinger does not conduct classified research.

- Human testing of chemical or biological agents, except for certain prophylactic, protective or peaceful purposes.

4.2 DoD Limitations on Waivers of Informed Consent and Consent by LARs

The requirement to obtain consent cannot be waived for any research using DoD funds and meeting the definition of research involving a human being as an experimental subject (10 USC 980). This places limitations on research involving deception, decisionally-impaired individuals, or research being conducted under emergency conditions where the subject may not be able to provide consent.

This statute applies only to certain intervention studies. It does not apply to retrospective research involving analysis of data or specimens, observational studies, blood draws, or tissue collection, and does NOT apply to screening of records to identify possible subjects. The IRB may grant a waiver of consent for such activities.

The Secretary of Defense may waive this consent requirement for a specific project in order to advance the development of a medical product necessary to the Armed Forces, but only if the research may directly benefit the subject and the research is carried out in accordance with all other applicable laws and regulations.

Informed consent may be provided by a legally authorized representative (LAR) only if: (1) the subject lacks decision-making capacity; AND (2) the IRB has determined that the research is intended to be beneficial to the individual subjects.

4.3 Research Monitor for More than Minimal Risk Research

A research monitor must be appointed for all research that involves more than minimal risk. The monitor may be either a medical or non-medical monitor depending on the nature of the research. The monitor must be independent of the research team and possess sufficient expertise to evaluate the risks and conduct of the research. The investigator must identify a research monitor by name and have the selection approved by the reviewing IRB. The IRB may choose to appoint more than one monitor for a project and may choose to appoint a monitor for research that is deemed to be no more than minimal risk.

The duties of the monitor are determined based upon the specific risks or concerns associated with each research project. Examples of monitor activities include assessment of subject recruitment and enrollment, data collection or data storage, and analysis. The monitor may be asked to discuss research progress with the investigator, interview subjects, or evaluate adverse events. The monitor has the authority to stop a study in progress, remove participants from the study, or take necessary steps to protect the safety and well- being of participants until the IRB can assess the study.

The IRB must document the required duties and responsibilities of the monitor and communicate this information to the monitor.

The Institutional Official of the DoD Component may waive the requirement for the monitor.

4.4 Vulnerable Populations

DoD requires that the protection of Common Rule subpart B (Pregnant Women/Fetuses), C (Prisoners), and D (Children) be applied to the research it supports. See DoD Instruction 3216.02, Part 7, for a description of additional DoD considerations for these populations. The DoD (and the IRB) considers the need for similar safeguards for other vulnerable populations such as those with cognitive impairment, or any other circumstance that might require special protections.

Section 5 below describes protections for military personnel as research subjects.

4.5 DoD Protections from Medical Expenses if Injured

For more than minimal risk research, the informed consent document must provide information regarding payment of medical expenses, provision of medical care, or compensation for research-related injuries, consistent with the requirements of the Common Rule.

5. DoD Personnel as Research Subjects

5.1 Military Participants

- Adult Status: All active duty service members and reserve component members are considered to be adults for the purpose of participating in DoD-conducted or supported research.

- Command Approval: Command approval may be required for military personnel to participate in human subjects research as some types of research could impact a soldier's readiness in the field. Investigators may be asked to provide documentation of Command approval as part of the IRB review.

- Protection of Service Members from Undue Influence: Officers and senior non-commissioned officers may not influence the decision of subordinates to participate in human subjects research and may not be present at the time of recruitment. Superior officers must be recruited in a separate session from subordinates.

For more than minimal risk research and where recruitment is conducted in a group setting, an ombudsman must be present to ensure that information is clearly, accurately and adequately presented and that the voluntary nature of participation is emphasized. The ombudsman may be the same individual appointed by the IRB as the research monitor.

5.2 DoD Civilian Personnel

DoD civilian personnel who are recruited into research are afforded the same protections as military personnel (5.1 above). The requirement for an ombudsman is at the discretion of the IRB.

5.3 Limitations on Compensation

On-duty federal personnel including military members:

- Up to $50 for blood draws;
- Compensation is not allowed for general research participation.

Off-duty federal personnel including military members:

- Up to $50 for blood draws;
- Compensation is allowed for general research participation, as approved by the IRB. Payment many not come directly from a federal source. Payment from a federal contractor or non-federal source is permissible.

Non-federal personnel:

- Up to $50 for blood draws;
- Compensation is allowed for general research participation, as approved by the IRB. Payment may come from a federal or non-federal source.

6. Other DoD-Specific Requirements

6.1 Reporting Requirements

The following must be promptly reported to the HRPO of the DOD Component (within 30 days of the event):

- Determinations of serious or continuing noncompliance;
- Unanticipated problems involving risks to subjects or others;
- Study suspensions or terminations;
- Audits, inspections or investigations of DoD research;
- Results of Continuing Review;
- Changes to the reviewing IRB;
- Substantive modifications to the research protocol including: a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design that would prompt additional scientific review, or a change that could potentially increase risks to subjects. Amendments must be reviewed and approved by the HRPO prior to implementing the change to the study.

6.2 Record Keeping

Consistent with Geisinger's policy, research records must be maintained for at least 3 years after the completion of the research. Signed Research HIPAA Authorization must be maintained for 6 years. The DoD may require that research records be transferred to the DoD Component rather than being retained by Geisinger.

ATTACHMENTS:

Major DoD Components

Department of Defense (DOD) Sponsored Research: Investigator Responsibilities

REFERENCES:

DoD Regulations and Guidance
32 CFR 219, Protection of Human Subjects
10 USC 980, Limitations on the Use of Humans as Experimental Subjects
DoD Instruction 3216.02, Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research
DoD Instruction 3210.7 Research Integrity and Misconduct
DoD Instruction 6200.2, Use of Investigational New Drugs in Force Health Protection

DoD Component Requirements
Office of the Secretary of Defense for Personnel and Readiness (download)
HA Policy 05.003: Policy for Protection of Human Subjects in Department of Defense Sponsored Research

Department of the Army
AR 70-25: Use of Volunteers as Subjects of Research AR
AR 40-38: Clinical Investigation Program
AR 40-7: Use of U.S. Food and Drug Administration-Regulated Investigational Products in Humans including Schedule I Controlled Substances

Department of the Navy
SECNAV Instruction 3900.39D, Human Research Protection Program, November 6, 2006
Department of Navy, Training and Education Guidance, March 2013

Department of the Air Force
Air Force Instruction DODI3216.02 AFI40-402: Protection of Human Subjects and Adherence to Ethical Standards in Air Force Supported Research.

*** The DoD regulatory and guidance resources cited here are key resources regarding the conduct of DoD-related human subjects research. This is not intended to serve as an authoritative list of all regulations or guidance that may apply to such research. The sponsoring DoD Component can provide additional information.**

Attachment A – Major DoD Components**

- Air Force
- Air Force Academy
- Air Force Office of Scientific Review (AFOSR)
- Army
- Army Corps of Engineers
- Army Medical Research and Material Command (USAMRMC)
- Army Research Lab
- Army Research Office
- Coast Guard
- Coast Guard Academy
- Congressionally Directed Medical Research Program (CDMRP)
- Defense Advanced Research Projects Agency (DARPA)
- Defense Intelligence Agency
- Defense Medical Research and Development Program (DMRDP)
- Marine Corps
- Military Academy (West Point)
- Missile Defense Agency
- National Geospatial-Intelligence Agency
- National Guard
- National Security Agency
- National War College
- Naval Academy
- Navy
- Office of Naval Research (ONR)
- Pentagon Force Protection Agency
- Tricare Health System
- U.S. Naval Observatory

** This is not a comprehensive list of DoD Component entities.

Department of Defense (DOD) Supported Research:

Investigator Responsibilities

Investigators who conduct research supported by the Department of Defense (DOD), including collaboration with DOD, or involving DOD facilities or personnel (military or civilian), must follow additional regulatory requirements.

This checklist can be used as a resource to ensure investigators complete these additional DoD requirements. Please review at the time of initial IRB approval and annually until the research has concluded. For further information contact IRB staff at 570-271-8663 or irb@geisinger.edu.

STUDY INFORMATION	
Geisinger IRB #	
Study Title	
PI Name	

Before IRB Approval			
Requirement	**Yes**	**N/A**	**Documentation**
Review GIRB Policy - DOD Research Requirements	☐		
Check with the Program officer/ Scientific Contact at sponsoring DOD component about any additional requirements.	☐		

After IRB Approval			
Requirement	**Yes**	**N/A**	**Documentation**
Submit protocol and other required information to the *sponsoring DoD component Human Research Protections Office (HRPO)* for administrative review before beginning research activities.	☐		DOD HRPO Approval. **Note:** DOD HRPO Approval should be submitted to GIRB via Study Submission Response as part of the Pending Approval Process

During Conduct of Study			
Submit to the HRPO:	**Yes**	**N/A**	**Documentation**
Substantive amendments approved by the IRB. Examples: • PI change • Change or addition of an institution • Elimination or alteration of the consent process • Change to the study population that has regulatory implications • Significant change to study design, or changes that increase risk to subjects.	☐	☐	Communications with HRPO. Documentation of HRPO approval/acknowledgement Note: Communications, acknowledgements, and/or approvals from the DOD should be submitted to GIRB via Amendment/Modification Submission Response
Results of the IRB continuing review, on an annual basis	☐	☐	
If the IRB of record changes to a different IRB	☐	☐	
Determinations of serious or continuing non-compliance.	☐	☐	
All Unanticipated Problems Involving Risk to Subjects or Others/Unanticipated Problems	☐	☐	
Suspensions or terminations	☐	☐	
When the research is the subject of any federal department or agency audit, inspection, or investigation.	☐	☐	

If the study has a research monitor assigned, ensure that monit oring occurs as outlined in the protocol. Note: A research monitor is required for greater than minimal risk research.	☐	☐	Documentation of what was reviewed, when it was reviewed, who conducted the monitoring, and any findings or observations and their corrective actions. **Note:** Monitoring reports should be submitted to GIRB via Amendment/Modification submission
Record Keeping Requirements			
Requirement	**Yes**	**N/A**	**Documentation**
Retain research records per Geisinger record retention guidelines.	☐		