This Manual of Policy and Procedures has been established to formalize the policies of the Office of Human Research Protection of the Greenville Health System. The June 2017 edition of this manual supersedes previous editions. Additions, rescissions, revisions and corrections will be published as required.

The Medical Director of the Office of Human Research Protection will maintain the master copy of this manual. Individual copies will be kept current by means of issuance of revised or new policies as appropriate.
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1.0 PURPOSE

The Greenville Health System (GHS) is committed to performing high quality healthcare research that prioritizes protection of human subjects. To meet this standard, GHS will follow:

- Regulations issued by the DHHS at 45 CFR Parts 46 and 164;
- Regulations issued by the FDA at 21 CFR Parts 50, 56, 312 and 812;
- Belmont Report;
- Nuremburg Code;
- Declaration of Helsinki;
- International Conference on Harmonisation (ICH) Guidelines pertaining to ethical and quality standards for study design, conduct, performance, monitoring, auditing, analyses and reporting of clinical trials (Good Clinical Practice);
- South Carolina State Law

Completion of the eIRB smartform application and its questions concerning the applicability of rules regarding human subjects research determine GHS OHRP IRB’s level of involvement.

No human subject research may commence at GHS until the project is submitted to, and approved, by the GHS IRB or an IRB cooperating with GHS under the terms of the GHS Federal Wide Assurance and GHS HRPP Policy No.37.0. This will be accomplished by:

1. Educating investigators on the requirements to perform research involving human subjects;
2. Educating department leadership of the requirements for IRB approval before any research activities involving human subjects begin and teaching leadership how to verify the IRB has approved a research study;
3. Sanctioning investigators and/or departments conducting human subject research without IRB approval.

Heightened scrutiny in accordance with federal and state laws and regulations will apply to any research involving prisoners, pregnant women, children or those with diminished cognitive capacity.

Certain types of research are not conducted by the Greenville Health System.

1. Research involving prisoners;
2. Research involving populations where no translator is available and only a family member could provide translation;
The various departments at GHS including the Medical Staff, Nursing, Pharmacy, Allied Health components and the various educational programs will work cooperatively through the Office of Human Research Protection (OHRP) Policy and Procedures, the Impacted Services certification program and the requirement of departmental scientific review to ensure that patient safety and human subject protection are maximized. This process will include:

1. A listing of departments/services that are most likely to be affected by research studies included in the eIRB application form. The investigator must indicate all departments or services affected by the research study.
2. Departmental approval and sign off will be obtained prior to submission to the IRB. Once approval has been obtained, the eIRB application will automatically be submitted to the IRB. If the department approver requires additional information the eIRB application will be sent back to the PI requesting additional changes and/or information.
3. Research cannot be submitted to the IRB that does not include all necessary approvals.

Greenville Health System administration and department heads will receive training on IRB review and approval requirements and will provide training to department or service staff members on those requirements. All Greenville Health System staff, research investigators, IRB members and IRB staff are expected to comply with federal regulations and IRB policies for the protection of human subjects in research and to notify the IRB Office of any violations or non-compliance with those regulations and policies.
1.0 PURPOSE

All individuals involved with the human research protection program are expected to understand and apply their ethical obligation to protect the rights and welfare of research participants. Individuals particularly obligated to this charge include the following: Researchers and research staff (including students involved in the conduct of research), IRB Members and Chairs, IRB staff, the Institutional Official, IRB Coordinators, IRB staff, the OHRP Medical Director, the OHRP Director, GHS employees, and students.

The purpose of the Greenville Health System (GHS) Office of Human Research Protection (OHRP) Human Research Protection Program (HRPP) is to protect the rights and welfare of human subjects of research, and assure investigators conduct clinical research according to corresponding federal regulations, state law, and OHRP HRPP policies. GHS OHRP advances this purpose through the GHS OHRP HRPP Policies and Procedures.

These policies also apply to research at entities designating Greenville Health System IRB as their IRB of record under a Federalwide Assurance.

The Administrative Official and the Chairperson(s) shall continuously review the OHRP HRPP Policy and Procedures. All amendments and/or revisions shall be forwarded to the Institutional Official, for approval, prior to implementation.

ORGANIZATION

A. Components of the Office of Human Research Protection and roles and responsibilities:

The Greenville Health System organizes the Office of Human Research Protection (OHRP) in a manner facilitating independent surveillance of human research participant protection. GHS’ designates three IRB Committees to oversee particular emphasis areas (Committee A=Adult, Non-Oncology studies; Committee B=Pediatric studies; Committee C=Adult Oncology studies). A medical staff Committee Chair, accompanied by an IRB Coordinator, staff each committee to facilitate the review of proposed research.

The OHRP Director supervises the staff of the OHRP, coordinating with the OHRP Medical Director. They collectively assume responsibility for the ethical review of all
studies proposed in the Greenville Health System. OHRP monitors all investigators to ensure approved investigators conduct human subject research consistent with approved protocols, OHRP Policies and Procedures, and federal and other applicable guidelines and statutes.

B. Relationship among the components:

The components of the OHRP communicate and work together to protect research participants. The OHRP Director, Chief Science Officer, and OHRP Medical Director lead the development of OHRP policy. The Chief Science Officer (as Institutional Officer) and the OHRP Medical Director assume final signatory authority/approval of OHRP Policies and Procedures. The OHRP Director is responsible for OHRP administrative oversight, and Coordinators report to the OHRP Director. The OHRP Medical Director is additionally responsible for safeguarding the biomedical propriety of proposed work. Medical Chairs of each Committee report to the OHRP Medical Director. The OHRP Medical Director acts as a quasi-independent authority to ensure autonomy and protection from undue influence germane to research ethics considerations.

The OHRP Director supervises the staff of the OHRP, coordinating with the OHRP Medical Director. OHRP is one of the research administrative functions of the GHS Health Science Center reporting to the GHS Chief Science Officer, ultimately reporting to the GHS Chief Academic Officer. The Chief Science Officer (as Institutional Officer) is OHRP’s representative in extramural matters. This reporting structure ensures all GHS research concords with/support GHS ’academic mission and vision. Reciprocally, OHRP leaders are positioned to directly inform the Chief Academic Officer of IRB-approved research, trends, and opportunities poised to advance evidence-based medical practice and policy.

The Corporate Compliance Office is empowered to audit OHRP to ensure research compliance with Federal Guidelines. The Corporate Compliance Office reports directly to the Vice President and Chief Financial Officer to ensure autonomy from OHRP. This reporting structure better ensures audits without undue influence from OHRP or investigators.

All noted stakeholders ultimately report to the Greenville Health System’s President, the governing authority in the Greenville Health System. In IRB-related matters, the OHRP Medical Director informs and consults with the President. The autonomy of the Medical Director’s office ensures unbiased assessment of research propriety, and undue influence over research approval and subsequent conduct.

RESOURCE ASSURANCE
To ensure OHRP fulfills the charge described above, the Greenville Health System Board of Trustees and President commit to providing OHRP resources essential to its mission via the Chief Science Officer/Institutional Official and medical staff leadership (referred to below as “leadership”). This includes, but is not limited to:

- **Requisite workspace** - leadership will provide OHRP a designated and exclusive workspace to perform duties of the office. The workspace is designed/tailored to facilitate ethical study review, investigator and participant confidentiality, and OHRP protection from undue influence.

- **Personnel** - leadership will ensure the workforce necessary for OHRP to conduct appropriate internal review and oversight, or delegate study review to an external IRB. This may include administrative and medical staff oversight, committee coordinators and committee membership. (see OHRP Policy and Procedures Policy No. 5.0)

- **Legal Counsel** - leadership will grant access to the Greenville Health System legal expertise to ensure compliance with federal and state guidelines.

- **Conflict of interest** - leadership empowers OHRP personnel to review and evaluate potential conflicts of interest in conduct and review of research/proposed research (see OHRP Policies and Procedures Policy No. 6.0; 9.0, Sect. 2.1 b). Leadership also empowers a Conflict of Interest committee that includes the Executive Director of Corporate Integrity and the ORHP Medical Director.

- **Quality Improvement** - leadership provides technical resources to survey IRB users (e.g., investigators, participants) on OHRP services so that the office periodically assesses OHRP functions to determine appropriate improvement in services.

- **Community outreach** - leadership provides technical resources (e.g., web survey, telephone contact) allowing community stakeholders and research participants to note concerns or comments.

- **Internal Review Board (IRB)** - leadership empowers OHRP to recommend, recruit and designate IRB committee members (see OHRP Policies and Procedures Policy No. 5.0).

**RESOURCE EVALUATION**

The OHRP Director is responsible for evaluating resources at least once annually (e.g., annually, or as needed). Resource evaluation includes, but is not limited to budget, workspace, personnel. The OHRP Director and Medical Director may request budget modification, space and personnel needs via the Institutional Officer and the Executive Director of Business and Finance. The OHRP Director and Medical Director will reference benchmark metrics and institutional needs to assess and recommend workspace, personnel and budget. The annual review process and resultant decisions and institutional action will be documented.

**2.0 ETHICAL PRINCIPLES**

The GHS IRB applies the *Belmont Principles* to its deliberations and decision-making in its goal to protect the rights and welfare of human subjects of research, while applying federal regulations and state laws to human research.
The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral, and published in 1979 delineates the ethical principles for the conduct of human research upon which the federal regulations are based.

Those principles are:
- **Respect** for persons to involve recognition of the personal dignity and autonomy of individuals, and special protection of those persons with diminished autonomy.
- **Beneficence** to entail an obligation to protect persons from harm by maximizing anticipated benefits and minimizing possible risks of harm.
- **Justice** to require that the benefits and burdens of research be distributed fairly.

2.1 Compliance with these principles is carried out in the following manner:

A. Investigators and research staff may not commence human-subjects research prior to obtaining IRB and, as appropriate, other institutional approval of their protocols. Principal Investigator status is restricted to members of the GHS medical professional staff, nursing staff, employees of GHS, or a member of the faculty of one of the university partners affiliated with GHS. Professionals in training (i.e. medical students, nursing students, students of affiliate institutions, or resident physicians) are not permitted to be Principal Investigators. Fellows may be principal investigators if they have medical staff privileges at GHS. For each protocol submitted to the GHS IRB for approval, the PI must certify that s/he accepts responsibility for assuring adherence to applicable federal and state research regulations and hospital policies relative to the protection of the rights and welfare of subjects enrolled in the research.

B. IRB members and IRB staff are responsible for ensuring that the investigators:
   - Use procedures which are consistent with sound research design and which do not expose subjects to risks, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
   - Determine that risks to the subjects are reasonable in relation to the anticipated benefits to subjects, if any, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB member should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB member should not consider possible long-range effects of applying knowledge gained in the research.
   - Determine that selection of subjects is equitable.

C. In making this assessment, the following should be taken into account:
   - a) the purpose(s) of the research and the setting in which it is conducted; and
   - b) should be particularly cognizant of special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, cognitively or mentally impaired persons, or economically or educationally disadvantaged persons.
   - Determine whether the informed consent is adequate, and if not, request clarifications and changes in the consent form to adequately explain the purpose of the research, the risks and benefits entailed therein, and that it contains all other federally or locally mandated elements.
   - Determine that the research plan makes adequate provision for monitoring the data collected to ensure the safety of the subjects.
- Determine that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data.
- Ensure additional safeguards are in place to protect the rights and welfare of subjects that are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, cognitively or mentally impaired persons, or economically or educationally disadvantaged persons.

2.2 Investigators, research staff, IRB members, IRB staff, and the Institutional Official are required to read, and be familiar, with:
- The Belmont Report and the basics of ethical research;
- GHS OHRP Policies and Procedures.

OHRP will ensure information dissemination by posting OHRP Policies and Procedures manual online (located at: http://hsc.ghs.org/eirb/forms/). OHRP will inform stakeholders of policy changes via the following meetings: IRB committee reviews, GHS leadership and stakeholder meetings (e.g., Academic Council, Research Division Advisory Council).

2.3 Investigators, research staff, IRB members, IRB staff, and the Institutional Official are required to complete the CITI education course (or appropriate alternative education approved by the Medical Director of OHRP) prescribed by the GHS to include modules in:
- The Belmont Report;
- History of Human Subjects Research and Ethical Principles;
- Protection of Vulnerable Subjects;
- Conflicts of Interest.

2.4 Investigators, research staff, IRB members, IRB staff, and the Institutional Official are expected to:
- Conduct ethical research in accordance with The Belmont Report;
- Report ethical breaches in accordance with GHS HRPP Policy Number 20.0;
- Maintain accurate detailed and permanent records of research procedures and results;
- Comply fully with all policies, federal regulations and GHS guidelines governing the use of human, or animal, subjects or biohazardous materials.

3.0 SUGGESTIONS AND/OR CONCERNS OF PARTICIPANTS IN RESEARCH REVIEWED BY A GHS IRB

Additionally, the GHS OHRP Medical Director is responsible for soliciting and responding to the suggestions and concerns of participants in research reviewed by a GHS IRB or from any other member of the public or GHS medical personnel. GHS also provides, via the OHRP website (http://hsc.ghs.org/research-protection/), a telephone number contact for GHS’ IRB. Prospective, current, or past research participants may use the contact number to pose questions, comments, concerns, or obtain information on research-related risk or injuries.
Investigators with concerns or complaints about the service they have received from the GHS OHRP, or one of the IRBs, and have not been able to resolve the problem after direct communication with the GHS OHRP Medical Director, or the IRB, may address their concerns and/or suggestions by submitting a written document addressed to:

GHS Institutional Official  
Health Science Administration Building  
701 Grove Road  
Greenville, S.C. 29605.

The Institutional Official may respond verbally, or in writing, and may take such action necessary to address the concerns and/or suggestions.
Title: Definitions

RELEVANT DEFINITIONS – For Operational definitions not delineated in this Section, please refer to “Institutional Review Board Management and Function” by R Amdur and E Bankert, which is located in the IRB office.


Ad Hoc: for or concerned with one specific purpose or case; often improvised or impromptu.

Administrative Hold: a voluntary decision made by an investigator, even if prompted by a verbal or written recommendation from the IRB Chair or another institutional official, to suspend or terminate some or all activities being conducted under an IRB-approved research protocol pending further review or investigation by the IRB or other entity with the institution. This is not considered a suspension or termination of IRB approval.

Administrative Noncompliance: noncompliance that is administrative in nature (for example, submitting a report of an unanticipated problem a day late, submitting incomplete documentation).

Adult: is a human being age 18 years or older.

Adverse Event: any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research. Adverse events encompass both physical and psychological harms.

Age of Majority: age of majority is eighteen (18) years. For health services other than operations (unless operation is deemed essential to the health and life of the child): sixteen (16) years. Any married minor or spouse of the married minor can consent to diagnostic, therapeutic and postmortem procedures.

Agent: includes all individuals performing institutionally designated activities or exercising institutionally delegated authority or responsibility.

Allegations of Noncompliance: an assertion of noncompliance that has yet to be proved or supported by evidence.
**Alternate Member:** alternates are members appointed on any of the three (3) IRB committees. These members may substitute for another member on a different panel if his/her role (non-scientist or scientist) is comparable as determined by the IRB chairperson(s) and/or the OHRP Medical Director.

**Anonymized Samples (Unlinked):** unlinked samples are those that may have been acquired from identified human sources, but all identifiers or codes have been removed and destroyed such that the ability to identify particular individuals, via clinical or demographic information, would be extremely difficult for the investigator, the repository or a third party.

**Approval Period:** research involving human subjects may be approved for a maximum period of one year from the date of approval or a shorter period of time, if determined by the IRB. An IRB approval period expires on the last date that the protocol was approved.

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

**Assurance:** an agreement between an Organization and a federal agency that stipulates that the Organization will comply with regulatory requirements. 45 CFR 46.103

**Audit:** an independent review of a research study, (e.g. data, processes, investigator or team involved with human subject research). Audits are conducted by auditors according to set rules. Audits conducted by the GHS/OHRP HRP Auditor “sample” information and observe parts of a research study to determine if it is in compliance with federal and state regulations including, but not limited to, HIPAA, the Common Rule, FDA regulations, GHS OHRP, and GHS policies, as appropriate.

**Audit Plan:** a document that describes, in general terms the audit activities that will be undertaken. The GHS /OHRP audit plan lists all studies involving human subjects in a database to be audited with the rationale for the audits. The audit plan may change during the course of the year based on new information or changes in regulatory or OHRP, and/or standards.

**Audit Report:** a report, written by an auditor, in which the observations and findings of an audit are documented. The audit report provides key points to counsel, educate and help an auditee self-correct areas of noncompliance or potential noncompliance.

**Audit Schedule:** the audit schedule lists all research studies involving human subjects in the GHS Office of Human Research Protection anticipated to be audited with the rationale for the audits. The audit schedule is developed by the GHS OHRP auditor on a semi-annual basis.

**Auditee:** the department, investigator, or research team to be audited.

**Auditor:** a person trained in research that has undergone special training on regulatory agency standards and guidelines and auditing techniques. For the purposes of the SOP, the auditor is also knowledgeable in GHS OHRP and/ policies. The HRP Auditor is independent from the research area, is employed by GHS/OHRP, and reports to the GHS Executive Director of Corporate Compliance. The HRP Auditor performs audits on human research subject for all research studies approved by the GHS IRB’s (Institutional Review Committees).

**Authorization:** express written permission that an individual permits the release and use of their individually identifiable health information for a particular purpose. Authorizations are not required to use an individual’s health information to treat them, obtain payment or for a provider’s health care operations. However, under
HIPAA, research is not considered health care operations, and therefore requires an authorization or waiver of authorization with limited exception. The provider (or investigator) is responsible for obtaining an authorization from an individual.

**Benefit:** the positive value or advantage of being part of the research study. This value or advantage might be concrete for individual subjects, like a greater chance of having a good therapeutic outcome. Alternatively, it might be more intangible and general. For example, the results from a study could be crucial to understanding the underlying socioeconomic causes of drug addiction.

**Business:** any corporation, partnership, sole proprietorship, firm, franchise, association, organization, holding company, receivership, business or real estate trust, or any other legal entity organized for profit or charitable purposes, but excluding the Greenville Health System, any affiliated hospital, any Private Medical Practice or any other entity controlled by, controlling, or under the control of the Greenville Health System.

**Children/Minors:** according to the federal regulations, 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 South Carolina, any human being under the age of 18 years is a child.

**Clinical Investigations:** 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 submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

**Clinical Research:** any research or procedure involving human subjects in vivo or the use of human samples for the development and evaluation of patient therapies such as diagnostic tests, drug therapies, or medical devices. It includes early clinical studies, epidemiological studies and clinical trials. It does not include a Faculty Member’s participation in the design of a clinical study for which he/she is subsequently neither a participant nor an author.

**Coded Samples:** are those from which the source of the specimen can be identified by reference to a code rather than a name or other personal identifier. When such samples are obtained from a tissue repository, the repository retains information linking the code to a particular human specimen. Information is sufficient such that the investigator, repository or third party could link the biological sample or information derived from the research using the sample with a particular person or small group of identifiable individuals.

**Collector-Investigator:** persons charged with the responsibility of obtaining specimens from subjects for the purpose of adding to a repository.

**Community-Based Participatory Research (CBPR):** a partnership approach to research that equitably involves, for example, community members, organizational representatives, and researchers in all aspects of the research process, in which all partners contribute expertise and share decision making and responsibilities.

**Conduct at or on behalf of:** human subjects research that is conducted at this institution’s facilities or property; is sponsored by this institution, is conducted by or under the direction of any employees or agents of
this institution in connection with the institutional responsibilities, or involves the use of this institution’s non-public information to identify or contact human research subjects or prospective subjects.

**Confidentiality:** the assurance that certain information that may include a subject’s identity, health, behavior, or lifestyle information or a Sponsor’s proprietary information would not be disclosed without permission from the subject (or sponsor). Confidentiality is a means of protecting one’s privacy.

**Conflict of Interest:** means that because of activities or relationships with other persons or organizations, an individual is unable, or potentially unable, to remain impartial, that the individual’s objectivity is, or might be otherwise impaired, or that the individual has, or might acquire, an unfair competitive advantage. Information that is relevant to a conflict of interest determination includes stock holdings and investments of the individual, the individual’s spouse, and children or significant other; current positions held or under negotiation; any other sources of income; involvement in the design, conduct, or reporting of the research and any other relevant information that may have a bearing on the individual’s proposed participation.

**Conflict of Interest (IRB Membership, Research Investigators and Research Staff):** conflict of interest means that because of activities or relationships with other persons or organizations, an individual is unable or potentially unable, to remain impartial, that the individual’s objectivity is, or might be otherwise impaired, or that the individual has, or might acquire, an unfair competitive advantage. Information that is relevant to a conflict of interest determination includes stock holdings and investments of the individual, the individual’s spouse, and children; current positions held or under negotiation; any contracts, grants or cooperative research and development assignments the individual is working on or has under negotiation; any other sources of income; and any other relevant information that may have a bearing on the individual’s proposed participation.

**Conflicts of Interest Which Must Be Disclosed by Investigators:** compensation made to the investigator in which the value of compensation could be affected by study outcome; a proprietary interest in the tested product, including, but not limited to, a patient, trademark, copyright or licensing agreement; any equity interest in the sponsor of a covered study, i.e., any ownership interest, stock options, or other financial interest who value cannot be readily determined through reference to public prices; any arrangement where the value of the ownership interests would be affected by the outcome of the research or ownership interests that exceeds 5% interest in any one single entity when aggregated for the immediate family. This requirement applies to all covered studies, whether ongoing or completed; any equity interest in a publicly held entity, or non-publicly traded entities, that exceeds $5,000 in value. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for 1 year following completion of the study; and significantly payments of other sorts, which are payments that have a cumulative monetary value of $5,000 or more made by the sponsor of a covered study to the investigator or the investigator’s institution to support activities of the investigator exclusion of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following completion of the study.

**Consent/Permission:** the agreement of the participant or the parent(s) of or guardian to the participation of their child or ward in the research/clinical investigation.

**Continuing Noncompliance:** means any noncompliance that occurs repeatedly after appropriate remedial education or corrective action has been instituted taking into consideration all relevant factors, including, for example: (1) whether the continuing noncompliance was intentional, or (2) whether the investigator collaborated in remedial activity and the continuing noncompliance was not intentional.
**Corrective Actions:** suggestions for corrections or improvements to be made to assure regulatory agency inspection readiness and alignment with regulations and standards and a listing of current good practices.

**De-Identified:** health information is de-identified if there is no reasonable basis to believe that the data can be used to identify an individual, or if the provider has no reasonable basis to believe it can be used to identify the individual. The Privacy rule requires one of the two following approaches to de-identify data:

If a person with appropriate knowledge and experience applying generally accepted statistical and scientific principles and methods for rendering information not individually identifiable makes a determination that the risk is very small that the information could be used, either by itself or in combination with other available information, by anticipated recipients to identify a subject of the information.

**OR**

If all 18 identifiers have been removed, including name, all geographic subdivisions smaller than a State including street address, city, county, precinct, zip codes and equivalent geocodes, (except for the initial 3 digits of a zip code if more than 20,000 people reside in the area), all dates including birthdays (other than the year) and ages over 89, phone numbers, fax numbers, email addresses, social security numbers, medical record numbers, health plan beneficiary numbers, account numbers, certificate/license numbers, vehicle identifiers and serial numbers (including license plate number), device identifiers and serial numbers. URLs, IP addresses, biometric identifiers, full face photographic images and any comparable images, any other unique identifier, characterstic or code: Note: Other demographic information, such as gender, race, ethnicity, and marital status are not included in the list of identifiers that must be removed.

**Dissent:** an individual’s negative expressions, verbal and/or non-verbal that they object to participation in the research or research activities.

**Donor-Subjects:** participants in research studies who give specimens to investigators for placement in repositories.

**Electronic Media:** the mode of electronic transmission. It includes the Internet (wide-open), Extranet (using Internet technology to link a business with information only accessible to collaborating parties), leased lines, dial-up lines, private networks, and transmissions that are physically moved from one location to another using magnetic tape, disk, or compact disk media.

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

**Encryption:** the process of converting information, particularly information such as social security number and name that identifies individuals, into a code.

**Engaged in Research:** an institution becomes “engaged” in human subjects research when its employees or agents (i) intervene or interact with living individuals for research purposes; or (ii) obtain individually identifiable private information for research purposes. 45 CFR 46.102(d),(f)

**Executive Session:** (for purposes of this policy) a session of the IRB that is closed to the public.

**Exempt:** research activities involving very little associated risks, and the sole involvement of human subjects will be in one or more of the categories listed in 45 CFR 46 (b)(1-6) or 21 CFR 56.104.

**Expedited Review Process:** research activities involving no more than minimal risk to human participants and involve only procedures listed in Section XIV “Expedited Review Procedure” categories may be reviewed by the IRB through the expedited review procedure. 45 CFR 46.110 and 21 CFR 56.110
Experienced: an individual(s) are wise and skillful in a particular area.

**Experimental subject (research involving a human being as an experimental subject):** An activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Research involving a human being as an experimental subject is a subset of research involving human subjects. This definition relates only to the application of section 980 of Reference (g); it does not affect the application of part 219 of Reference (c). This definition does not include activities that are not considered research involving human subjects, activities that meet the exemption criteria at section 219.101(b) of Reference (c), and research involving the collection or study of existing data, documents, records, or specimens from living individuals.

**Facilitated Review:** the review process used by local IRBs as they make the determination whether or not to accept the CIRB’s review of a study. The CIRB has the responsibility of conducting a full board initial review. The CIRB has the ability to request changes in the protocol and model informed consent document in an effort to improve human subject’s protection. The CIRB also has the responsibility for review of the following: amendments, both those requiring full board review or expedited review; continuing reviews; recruitment or educational materials intended for use by current or potential study participants; and review of unanticipated problems and serious adverse events distributed by the Sponsor to investigators.

Once the CIRB has approved a study, IRBs from institutions enrolled in the CIRB Initiative are able to perform a facilitated review and open the study in a much shorter time than required by the traditional local full board IRB review process.

**Federal Wide Assurance (FWA):** a document that fulfills the requirements of 45 CFR 46 and is approved by the Secretary of Health and Human Services.

**Financial interest:** is an interest in a Business consisting of: (1) any stock, stock option or similar ownership interest in such Business, but excluding any interest arising solely by reason of investment in such Business by a mutual, pension, or other institutional investment fund over which the Faculty Member does not exercise control; or (2) receipt of, or the right or expectation to receive, any income from such Business (or from an agent or other representative of such Business), whether in the form of a fee (e.g., consulting), salary, allowance, forbearance, forgiveness, interest in real or personal property, dividend, royalty derived from the licensing of Technology, technology transfer, patents, gifts, rent, capital gain, real or personal property, or any other form of compensation, or any combination thereof whose value exceeds $5,000.

**Financial Interest Related to the Research:** means financial interest in the sponsor, product or service being tested, or competitor of the sponsor or product or service being tested.

**Finding of Noncompliance:** noncompliance that is proven or supported by evidence.

**Genetic Research:** research (not diagnostic testing) which involves either the analysis of human chromosomes or DNA from an individual and/or family members for the purpose of deriving information concerning the individual or family about the presence, absence or mutation of genes, DNA markers or inherited characteristics or other studies with the intent of collecting and evaluating information about heritable diseases and/or characteristics within a family.

**Greater than Minimal Risk:** the probability and magnitude of harm or discomfort anticipated in the research are greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
Guardian: an individual who has received an order from a probate court to act on behalf of a study subject.

HIPAA: the Health Insurance Portability and Accountability Act of 1996. Also referred to as the Privacy Rule.

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 (as defined in 45 CFR 46.102(f). The FDA defines “human subject” as an individual who is or becomes a participant in research, either as a recipient of a 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.

Human Subject’s Research: any activity that (1) meets the DHHS definition of research and involves human subjects as defined by DHHS; OR (2) meets the FDA definition of research and involves human subjects as defined by FDA.

Human Subject Research Auditor (HSR Auditor): acting under the direction of the GHS OHRP Medical Director. The HRP Auditor will consult with and educate researchers who conduct human subject research in fulfilling their responsibilities to assure compliance.

Identified Samples: biological samples obtained by an investigator or a 3rd party which have identifiers attached or a link permitting determination of the individual subject source through the use of a code.

Identifiers: identifiers are information that can be used to link a sample or scientific result with a specific person or group of people. Examples of identifiers include name, social security number, hospital number or other unique identifier. It should also be noted that using current information technology, a combination of descriptive data may be sufficient to allow identification of the donor and thereby collectively may be considered identifiers (e.g. zip code, birth date or profession may be sufficient to identify a specific individual).

Immediate: occurring at once; instant.

Immediate Family: includes a member’s spouse, child, parent or legal guardian.

Immortalized Cell Line: a culture which is apparently capable of unlimited number of population doublings.

Informed Consent: the agreement to participate in research that is made voluntarily by an individual with legal and mental competence and the requisite decision-making capacity, after disclosure of all material information about the research. Informed consent means the knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion. Information conveyed in the informed consent/authorization procedure must include all essential elements listed in Section 13.0 of this manual.

Institutional Official (IO): an individual with the legal authority to represent the institution.

Institutional Review Board (IRB): any board, committee or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical and/or behavioral (general) research involving human subjects. The primary purpose of such review is to assure the
protection of the rights and welfare of the human subjects 21 CFR 56.102(g). The independent body is constituted of members with varying backgrounds (e.g. medical, nonscientific and unaffiliated).

**Interaction:** includes communication or interpersonal contact between the investigator (or a member of the research team) and the subject.

**Interested Member:** a member of the IRB who has Conflict of Interest in a research study being reviewed by the IRB.

**Intervention:** includes both physical procedures by which data are gathered (e.g. venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes.

**Investigational Device:** a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device any device not yet approved by the FDA for general use, or not yet approved for particular use being researched.

**Investigational Device Exemption (IDE):** the exemption by which the FDA permits a device that otherwise would be required to comply with a performance standard or to have pre-market approval, to be shipped lawfully in interstate commerce for the purpose of conducting investigations of that device 21 CFR 812.

**Investigational New Drugs (IND):** any research involving a drug, whether FDA approved or not, requires IRB approval. Drugs or drug combinations, which have not been approved, require an IND number from the FDA. The IND number must be clearly indicated on the IRB application. Approved drugs being studied for unapproved indications require either an IND or a waiver of the IND.

**Investigational Procedures:** any procedure tested for safety and effectiveness, not yet considered standard procedure for the particular use being researched.

**Investigators:** principal investigators and sub/co-investigators involved in the conduct of a research trial. The Food and Drug Administration (FDA) uses the term sub-investigators. For purposes of these policies the term co-investigator will be used. 21 CFR 50.3(d)

**IRB Action:** includes IRB discussion as a part of initial review, continuing review, expedited review, approval of revisions/amendments, consideration of adverse events, or authorization of emergency use or research; any IRB vote; and signing official documents (e.g., letters of approval, extension letters, or letters granting approval of revisions).

**IRB Approval:** (at GHS) means the determination of the IRB that the research has been reviewed and may be conducted at GHS, or affiliate where GHS is the IRB of record, within the constraints set forth by the IRB and by other Institutional and Federal requirements.

**Key Personnel:** key personnel are defined as all individuals responsible for the design or conduct of the study. Everyone who has contact with human subjects, with confidential data about human subjects, or data that obtained from human subjects, for research purposes is included.

**Legally Authorized Representative:** means an individual or entity 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. 45 CFR 406.402(c) 21 CFR 50.3(l). Under SC State Law and GHS policy a legally authorized representative is either a guardian appointed by the Court, an agent named in a health
care power of attorney, or a surrogate as defined in SC Adult Health Care Act (S.C. Code § 44-66, et. seq).

**Minimal Risk:** the probability or 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 [as defined by 45 CFR 46.102(i) and 21 CFR 50.3(k)]. In research involving prisoners, minimal risk is also defined as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons [45 CFR 46.303(d)]. Furthermore, the regulations state that the IRB must find that the risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers (45 CFR 46.305(a)(3)).

**Minimal Risk for Department of Defense Sponsored Research:** based on the phrase “ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests” shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g. frequent medical tests or constant pain).

**Minor Modifications:** minor modifications or changes do not include any procedures that involve more than minimal risk and the modification or change falls into categories (1)-(7) of research that could be reviewed using the expedited procedure.

**Minor Noncompliance:** means any noncompliance that is not serious or continuing noncompliance.

**Neonate:** means a newborn.

**Noncompliance:** means any failure to comply with any applicable federal, state, or local laws and regulations or the requirements or determinations of the GHS IRB, which include GHS IRB and institutional policies related to human subject protection.

**Nonscientific Member:** nonscientific member(s) may include individuals whose main concerns are unambiguously in nonscientific areas. Nonscientific members are individuals whose education, training, work, experience or other interests are not solely in medical, biological, or other scientific areas.

**Non-significant Risk (NSR) Device Study:** A study that does not meet the definition for a significant risk device study. NSR device studies should not be confused with the concept of “minimal risk.”

**Nonviable Neonate:** means a neonate after delivery that, although living, is not viable.

**OHRP:** means the Office for Human Research Protections. This is an office in the Office of the Secretary of Health and Human Services that is responsible for regulatory oversight of human subject research.

**Office of Human Research Protection (OHRP):** a department within the Greenville Health System responsible for providing oversight of the Institutional Review Board(s) (IRBs) and ensuring research compliance consistent with the United States’ Department of Health and Human Services’ Office for Human Research Protection.

**Parent:** a child’s biological or adoptive parent.
**Participant:** a living individual about whom a research investigator (whether a professional or a student) obtains data through intervention or interaction with the individual or from individually identifiable information. An individual who is or becomes a participant in research, either as a recipient of a test article or as a control. A participant may be either a healthy human or a patient. [45 CFR 46.102(f)] [21 CFR 50.3(g)]

**Participate:** means to be part of the described activity in any capacity, including but not limited to serving as the principal investigator, co-investigator, research collaborator or provider of direct patient care. The term is not intended to apply to individuals who provide primarily technical support or who are purely advisory, with no direct access to the data (e.g., control over its collection or analysis) or, in the case of clinical research, to the trial participants, unless they are in a position to influence the study’s results or have privileged information as to the outcome.

**Patient-Centered Outcomes Research (PCOR):** comparative effectiveness research explicitly and intentionally informed by patients’ stated perspectives on intervention value (e.g., potential outcome per cost), and preferences/priorities, per the intervention’s: benefits, harms, or alternatives.

**Patient Engagement:** meaningful involvement of patients, caregivers, clinicians, and other healthcare stakeholders throughout the research process—from topic selection through design and conduct of research to dissemination of results.

**Permission:** the agreement of parent(s) or guardian(s) to the participation of their child or ward in research and/or medical care.

**Pregnancy:** encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the presumptive signs of pregnancy, such as missed menses, until the results of pregnancy testing are negative or until delivery.

**Principal Investigator (PI):** has the ultimate responsibility for oversight of all research he/she is conducting and is ultimately responsible for all communication with the IRB (via the Office of Human Research Protection) regarding that research. The principal investigator accepts responsibility for training all personnel associated with the study in compliance with the human subjects regulations of 45 CFR 46.

**Prisoner:** any individual involuntarily confined or detained in penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing (45 CFR 46.303(c)).

**Privacy:** freedom from unauthorized intrusion.

**Private Information:** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

**Private Medical Practice:** means the professional services rendered by a physician, including departmental practice plans, and the procedures integral to those services.

**Proband:** the affected individual through whom a family with a genetic disorder is ascertained.
Prospective Study: a study designed to observe outcomes or events that occur subsequent to the identification of the group of subjects to be studied. Prospective studies need not involve manipulation or intervention but may be purely observational or involved only the collection of data.

Protected Health Information (PHI): individually identifiable health information transmitted by electronic media, maintained in any electronic media, or transmitted or maintained in any other form or medium.

Protocol: a formal plan that includes, at minimum, the objectives, rationale, design, methods and other conditions for the conduct of a research study (ICH-GCP).

Protocol Amendment: any change(s), clarifications, advertisements, (including minor consent form changes) made to the original protocol.

Protocol Deviation(s): any alteration/Modification to the IRB-approved protocol. The protocol includes the detailed protocol, protocol summary, consent form, recruitment materials, questionnaires, and any other information relating to the conduct of the research study.

Protocol Exception(s): any temporary protocol deviation that has been approved by the study sponsor prior to its initiation, e.g., enrollment of a subject who does not meet the eligibility criteria. [Note: Any permanent change to the protocol constitutes an amendment that must be submitted to the IRB for approval prior to initiation.]

Protocol Violation(s): any protocol deviation that is not approved by the IRB prior to its initiation or implementation.

Quorum: (for purposes of this policy) means a gathering of voting members of an Institutional Review Committee (more than half) that includes a physician, a non-scientific member, and one person not affiliated with the institution.

Recipient-Investigator: persons approved to receive specimens from a repository to use for research purposes.

Recusal: the temporary absence of the IRB member during the deliberation and vote on the project with respect to which the member has a conflict.

Repository: a common site for storage of collections of human biologic specimens available for study. This may be one geographic location or may be a virtual aggregation of biologic specimens from many locations. Repositories are also referred to as tissue banks, collections, resources, inventories, or by other terms. Repository activities involve three components: (i) the collectors of tissue samples; (ii) the repository storage and data management center; and (iii) the recipient investigators.

Research: a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge [as defined in 45 CFR 46.102(d)]. Activities, which meet this definition, constitute research for purposes of this policy, whether or not they are conducted or supported under a program, which is considered research for other purposes. For example, some demonstration and service programs may include research activities 45 CFR 46.102(d) or the creation or maintenance of a database or tissue storage bank for research purposes. For FDA research, see Clinical Investigation.

Research Certificates of Confidentiality: in situations where the Investigator requires protection of research of a sensitive nature, the principal investigator can apply to the Department of Health and Human Services to
protect this information. This allows a researcher to protect the privacy of research subjects by withholding from most persons not connected with the research team the names and other identifying information relating to research subjects. The protection will be granted only when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives. Examples include research relating to sexual attitudes, preferences, or practices, the use of alcohol, drugs, or other addictive products, pertaining to illegal conduct or to an individual’s psychological well-being or mental health, genetic information, information that, if released, could be damaging to an individual’s financial standing, employability, or reputation, and information that would normally be recorded in a patient’s medical record that, if released, could lead to social stigmatization or discrimination. Researchers may receive a Certificate of Confidentiality regardless of funding source. Researchers who receive a certificate may not be compelled by Federal, State or local legal processes or subpoenas to disclose information that they possess as a consequence of the research.

**Research Misconduct:** includes intentional, reckless or negligent failure to abide by applicable law, regulations, or IRB procedures; plagiarism; fabrication or intentional falsification of data, research procedures or data analysis; or other deliberate misrepresentation in proposing, conducting, reporting, or reviewing research. It does not include honest error or honest differences in interpretations or judgments of data. In cases of allegations involving activities submitted to or supported by a federal agency, the definition for misconduct specified in the agency’s regulations will apply.

**Residual Clinical/Diagnostic Specimens:** specimens obtained for routine patient care that would have been discarded if not used for research.

**Retrospective Study:** retrospective research studies are studies that utilize existing biological samples that have already been collected when the IRB request for approval is made. This may refer to biological samples collected for clinical indications and then stored (i.e. pathology specimens, left over sera, etc.) or a secondary use of biological samples collected previously for another research protocol (i.e. “leftover” sera from a research study or material in a tissue bank).

**Risk:** risks generally are evaluated according to the probability and magnitude of any harm that might occur. We can also quantify risk according to the magnitude of harm. Risks can also be classified according to their type. In medical research we often focus on physical risk. However, risks may also be social, legal, economic or psychological in nature. In addition, risks may apply to the individual subject or may apply to a broader segment of the society.

**Sample:** in context to this policy, a sample refers to any human biological material. This includes, but is not limited to, molecular material such as DNA, cells, tissue (blood, bone, muscle, etc), organs (liver, bladder, heart, etc.), gametes, embryos, fetal tissue, waste (hair, nail clippings, urine, feces, saliva, sputum, etc) and other materials of human origin.

**Scientific Member(s):** may include physicians and PhD level physical, biological or behavioral scientists, nurses, pharmacists, and other biomedical health professionals. Such members satisfy the requirement for at least one scientist.

**Scientific Misconduct:** means any fabrication, falsification, plagiarism, or other practice that seriously deviates from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research.

**Secretary:** the Secretary of the Department of Health and Human Services (DHHS) and any other officer or employee of the DHHS to whom authority has been delegated.
**Serious Noncompliance:** means any noncompliance that negatively impacts the rights and welfare of subjects or compromises the integrity of the study data.

**Serious Unanticipated Problem (SAE):** any event that results in death, a life-threatening situation, hospitalization or prolonged hospitalization, persistent or significant disability/incapacity or a congenital anomaly/birth defect or requires medical intervention to prevent one of the outcomes listed above. SAEs require prompt reporting to the Sponsor, the FDA and the IRB.

**Significant Risk (SR) Device Study:** a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health.

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

**Sponsor Investigator:** an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual e.g., it does not include a corporation or agency. [21 CFR 56.102(k)]

**Sponsored Research:** research that is commercially funded by a business enterprise (e.g., pharmaceutical company or device manufacturer); government sponsored research and/or private sponsored research.

**Standard Operating Procedures (SOPs):** (at GHS) documents that define in detail the underlying policies and the procedures for activities involved in the conduct of research involving human subjects.

**Study Staff:** research nurses and study coordinators that are involved in the research process, including but not limited to, patient recruitment, patient care, data collection and records completion.

**Subject:** as defined by FDA means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or have a medical condition or disease. [21 CFR 812.3(p)]

**Suspension:** means to cause some aspect of the research to be stopped temporarily or permanently while the research continues under review or an investigation takes place.

**Technology:** means any compound, drug, device, diagnostic, medical or surgical procedure intended for use in health care delivery.

**Term of Office:** refers to the length of time a person will serve in a particular office as a member, chairperson, or vice-chairperson.

**Termination:** means to cause the research to be stopped permanently in its entirety. Of note, expiration of GHS IRB approval is not considered termination of research.

**Term Limit:** a restriction that limits the number of terms a person may serve in a particular role on the IRB.
**Test article:** a drug or device that is being tested for safety and effectiveness, not yet approved by the FDA for general use, or not yet approved for the particular use being researched. 21 CFR 56.102(1).

**Unaffiliated Member:** has no affiliation with the Greenville Health System or its Human Research Protection Program, either self or family member. Unaffiliated member(s), who can be either scientific or nonscientific reviewers, should be knowledgeable about the local community and be willing to discuss issues and research from that perspective. Consideration should be given to recruiting individuals who speak for the communities from which the Greenville Health System will draw its research subjects. The unaffiliated member(s) should not be vulnerable to intimidation by the professionals on the IRB, and their services should be fully utilized by the IRB.

**Unanticipated Problem:** any unplanned occurrence that may affect the risks and/or potential benefits involved in the research study. Unplanned occurrences are usually related to study design or methods. Such occurrences can be favorable or unfavorable to participants and may or may not influence the study objectives or results (e.g., loss of confidentiality).

**Unexpected Unanticipated Problem (UAE):** any problem that was unanticipated or not previously observed (e.g., not included in the consent form or investigator brochure). This includes adverse events that occur more frequently or with greater severity than anticipated. Events that are unexpected and serious require prompt reporting to the Sponsor, the FDA and the IRB.

**Urgent:** compelling immediate action or attention.

**Viable:** as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintained heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the Federal Register guidelines to assist in determining whether a neonate is viable for purposes of this subpart. If a neonate is viable, then it may be included in research only to the extent permitted and in accordance with requirements of subparts A and subparts D of this part.

**Vulnerable Subjects/Participants:** mean individuals who lack the capacity to provide informed consent or whose willingness to participate in research may be subject to undue influence or coercion. Vulnerable subjects include, for example, children, prisoners, individuals with emotional or cognitive disorders/impairments and economically or educationally disadvantaged persons. 45 CFR 46.111(a)(3) 45 CFR 46.111(b) 21 CFR 56.111(a)(3) 21 CFR 56.111(b)

**Waiver of Authorization:** HIPAA permits waiver of authorization when an IRB reviews the request according to the required criteria. This review and approval of waiver of authorization requests must be documented.

**Ward:** a human being who is in the legal custody of any agency of the State of SC in departments such as the Department of Mental Health, Department of Social Services and the Department of Disabilities and Special Needs.
1.0 DEFINITIONS

*Engaged in Research:* for the purpose of this policy, investigators are considered “engaged” in human subjects research and come under the authority of the GHS IRB when they or their agents (i) intervene or interact with living individuals for research purposes; or (ii) obtain individually identifiable private information for research purposes. 45 CFR 46.102(d),(f)

*Systematic Investigation:* for the purposes of this policy, a 'systematic investigation' is an activity that involves a prospective research plan which incorporates data collection, either quantitative or qualitative, and data analysis to answer a research question.

*Generalizable knowledge:* for the purpose of this policy, investigations designed to develop or contribute to generalizable knowledge are those designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings."

The following are examples of activities that **would not** contribute to generalizable knowledge:

If a program evaluation, program assessment, or other activity is used **only** for:

- Internal improvements to a program or service.
- Quality assurance purposes (e.g., customer satisfaction surveys).

The following are examples of activities that **would** contribute to generalizable knowledge:

If a program evaluation, program assessment, demonstration project or other activity is:

- Conducted to examine whether the program had the desired effect on program participants, **and** that evaluation can inform other programs.
- Conducted with the intent to replicate the program.
- Designed to draw general conclusions.

2.0 SCOPE OF AUTHORITY DEFINED

The GHS OHRP IRB must approve all research or clinical investigations involving human subjects engaging GHS, its employees, its students, or its patients, as defined by the Office of Human Research Protections 45 CFR 46.102(d)-(f).
Research is defined as a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge (as defined in 45 CFR 46.102(d). Activities, meeting this definition, constitute research for purposes of this policy, whether or not they are conducted or supported under a program, which is considered research for other purposes. For example, some demonstration and service programs may include research activities 45 CFR 46.102(d), or the creation or maintenance of a database or tissue storage bank for research purposes. FDA includes in its definition of a research activity, any experiment that involves a test article and one or more human subjects and that either meets requirements for prior submission to the FDA or the results of which are intended for a research or marketing permit.

**Research that does not require IRB oversight**

1. Research that is not designated or intended to contribute to generalizable knowledge (i.e. no public presentations or publications outside of the institution will be made).

2. Activities, generally referred to as program evaluation or quality improvement, are not intended to have any application beyond the specific organization in which they are conducted. As is true in the area of public health, because populations are the subject of study and because the methods used in program evaluation or quality improvement are the same as those used in research, it is often difficult to determine whether an activity is research that falls under the oversight system.

3. Definitional issues regarding program evaluation or quality improvement are not limited to health care delivery. They also occur in industrial or educational settings and in social science and operations research. However, if the purpose is to assess the success of an established program, and the information gained from the evaluation will be used to improve that program, the activity should not be considered research involving human participants. Evaluation is a program monitoring tool, and the information gained will immediately benefit the program and/or the individuals involved.

However, when quality improvement involving human participants is undertaken to test a new, modified, or previously untested intervention, service, or program to determine whether it is effective and can be used elsewhere, the activity is human participant research and subject to the oversight system.”

For Food and Drug Administration (FDA) regulated research, clinical investigation is defined as any experiment that involves a test article and one or more human subjects and that is either subject to requirements for prior submission to the FDA, or the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit 21 CFR 50.3(c).

The Greenville Health System authorizes its IRB(s) to:

1. Approve, require modifications in (to secure approval), or disapprove all research activities submitted to it for approval.

2. Under the Privacy rule, the IRB may waive or alter, in whole or in part, the Privacy Rule’s Authorization requirements for the use and disclosure of PHI in connection with a particular research project. ([http://privacyruleandresearch.nih.gov/irbandprivacyrule.asp](http://privacyruleandresearch.nih.gov/irbandprivacyrule.asp))

3. Conduct continuing review of the research no less than once a year and require progress reports from study investigators at least annually.

4. Oversee the conduct of the research; this includes observing, or having a third party observe the consent process and the conduct of the research.
5. Suspend or terminate IRB approval of research that is not being conducted in accordance with the IRB’s requirements, or that has been associated with unexpected serious harm to subjects or any unanticipated problems involving risks to human subjects or others.

The IRB shall promptly report promptly to the GHS Institutional Official and OHRP Medical Director:

1. Any serious or continuing noncompliance by investigators with the requirements of the IRB.
2. Any suspension or termination of IRB approval; the investigators will also be so informed.
3. Any changes in IRB membership.

The Institutional Officer will additionally report the information above to GHS’ Board of Trustees and appropriate governmental officials when necessary/required.

3.0 STATUTORY BASIS FOR IRB AUTHORITY/REGULATORY AGENCIES

The GHS IRB is subject to regulation and inspection by all governmental regulatory agencies, including the Food and Drug Administration and the Department of Health and Human Services Office for Human Research Protections. In addition, the laws of the State of South Carolina also apply.

In some cases, International law may apply to the study. Any conflict between federal, state or national law must be referred to the GHS Legal office.

4.0 ORGANIZATIONAL STRUCTURE

The IRB(s) reports to the Institution by providing the Institutional Official (IO) with a copy of all IRB meeting minutes. Although the IRB reports to the IO, it retains autonomy in decision-making. IRB disapprovals, restrictions, or conditions cannot be rescinded or removed except by the action of the IRB.

Additionally, the administrative official meets regularly with the IO. The IRB Chairperson(s) meets with the IO as needed. The official policies of the IRB(s) are reviewed and approved by the GHS Board of Trustees.

Officials of the organization are prohibited from approving research that has not been approved by the IRB.

5.0 INSTITUTIONAL OFFICIAL

GHS has an approved Federal Wide Assurance (FWA) on file with the Office for Human Research Protections (OHRP), Department of Health and Human Services (DHHS). The FWA has been signed by an individual with the legal authority to represent the institution. This individual is referred to as the Institutional Official (IO).

The IO understands the institution’s responsibilities under the FWA, assures the protection of human subjects of research, and assures that the designated IRB(s) are knowledgeable about the local research context and will comply with the terms of the FWA. The FWA has been approved by OHRP and is updated as necessary when information changes.

The IO is responsible for:

- generating an institutional culture of respect for human subjects; including advocating for resources needed for the HRPP, including but not limited to:
• Ensuring effective institution-wide communication and guidance on human subject issues;
• Ensuring that investigators fulfill their responsibilities;
• Serving as a knowledgeable point of contact for OHRP.

Administratively, the IO is responsible for:

• Providing the IRB with necessary resources and staff; and
• Supporting the authority and decisions of the IRB.
• Reviewing the performance of the IRB Chairperson(s) at least annually and providing feedback.

6.0 GHS INSTITUTIONAL REVIEW BOARDS

The Greenville Health System has three IRB committees. Each committee has the following scope of research it reviews; however, at the discretion of the Medical Director, any study(ies) may be assigned to one of the three (3) IRB committees.

Greenville Health System IRB#1 – reviews Cardiology, Vascular Surgery, Plastic Surgery, Orthopaedics, Neurology, Nursing, Women’s, HIV/Infectious Diseases, Internal Medicine, General (non-pediatrics/nononcology).

Greenville Health System IRB#2 – reviews all adult oncology studies

Greenville Health System IRB#3 – reviews all pediatric studies, Women’s, Orthopaedics, Internal Medicine, HIV/Infectious Diseases, Neurology, General (non-adult oncology).

7.0 MULT-INSTITUTIONAL REVIEW

For research conducted at GHS and concurrently at another institution(s), the GHS IRB requires review and approval of full protocol (including recruitment documents) and consent forms. In general, the IRB can waive IRB standard language or formatting elements if participants are not recruited at GHS or GHS has no participant contact. GHS IRB will also review amendments, serious and/or unexpected adverse events, and protocol deviations. Each IRB that reviewed the protocol must be notified of any protocol changes, serious adverse events or other reportable events occurring at any site. Continuing Review is to be conducted in accordance with 45 CFR 46.109(e) and 21 CFR 56.109(f).

The GHS IRB is responsible for the protection of the rights and welfare of human subjects at the Greenville Health System, as well as research conducted at other locations by the GHS faculty and staff. There are standing cooperative agreements with other institutions whereby the GHS IRB has the authority over, and is responsible for, research at those institutions. The GHS IRB may function as the IRB of record for another investigator and/or institution but the other institution must apply for and receive a Federal Wide Assurance (FWA) of Protection for Human Subjects that designates GHS as the IRB on record filed at the Office for Human Research Protections (OHRP). In addition, an
Authorization Agreement must be signed, and a copy of the approved FWA must be submitted to the GHS IRB. The FWA must be renewed every five years.

Any IRB relied upon by GHS must meet the criteria defined in GHS HRPP Policy37.0.

8.0 HEALTH SCIENCES OF SOUTH CAROLINA (HSSC) IRB CO-OPERATIVE REVIEW

Pursuant to the “Cooperative Agreement – Institutional Review Boards” signed September 2006 by the HSSC ‘Collaborating Institutions’, Greenville Health System utilizes the eIRB cooperative services of HSSC. Other partner institutions of HSSC are Medical University of South Carolina (MUSC), University of South Carolina (USC), Palmetto Health (PH), Clemson University (CU), and Spartanburg Regional Healthcare System (SRHS). Each collaborating institution, through its OHRP-approved FWA, has designated reliance upon each of the other institutions’ IRB(s). This reliance allows the institutions to cooperate in human research studies while avoiding duplication of effort with respect to IRB reviews.

PURPOSE:
To facilitate research conducted at HSSC institutions when two or more collaborating institutions are involved in the same research project by streamlining the IRB process.

KEYWORDS:
IRB, eIRB, Principal Investigator, PI, IRB Coordinator, Primary IRB institution, Cooperative Review, Collaborating institution

PROCESS:
1. A Cooperative Review is initiated when the PI answers the following questions during the application process:
   a. Does this study involve multiple institutions (non-affiliated sites)?
   b. By answering YES, the next Smart Form asks:
      o If the research study will be conducted at any other Health Sciences South Carolina (HSSC) site(s), check all that apply.
      o If conducted at other HSSC site(s), is cooperative review by the other HSSC IRB(s) requested? Note: For all collaborative studies involving HSSC institutions the GHS or MUSC IRB will function as the IRB of record due to their AAHRPP accreditation status.

2. Upon approval by the primary institution’s IRB, email notifications are sent to the Lead IRB Coordinators at the collaborating institution(s) instructing them to review the cooperative study.

3. A list of requested Cooperative Reviews will be displayed under a “Cooperative Review Status” tab on the Study Workspace. Approval status for each collaborating institution(s) will be displayed under this tab.

4. All Cooperative Review studies will be in the collaborating institution(s) IRB Coordinator’s home page (In a new tab, Coop Studies).

5. All IRB coordinators of the collaborating institution(s) will be given read only access to full study application once Cooperative Review is requested.
6. A collaborating institution’s IRB committee, and all of its members, may be given read only access.
7. The following activities will be available to each collaborating institution.
<table>
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| Collaborating Institution’s IRB Coordinator and Collaborating Institution’s IRB Designated Reviewer | **Log Public Comments** - Adds a message to the history log on the study that all users can see.  
**Log Private Comments** - Adds a message to the history log on the study. Only users that are part of the IRB can see these messages. Assume that Private Comments will be viewable by IRBs at all collaborating institutions. |
| Collaborating Institution’s IRB Coordinator | **Request Cooperative Review** – Assign up to two Committee Members/Chairs to conduct Cooperative Review. |
| Collaborating Institution’s Designated Reviewer | **Submit Cooperative Review** – Designated reviewer selects appropriate motion – accept, reject, or request additional information. |
| Collaborating Institution’s IRB Coordinator | **Select Cooperative Committee** - Allow access to a collaborating institution’s IRB Committee. |
| Collaborating Institution’s IRB Coordinator | **Record Cooperative Decision** – Allows collaborating institution’s IRB Coordinator to make a motion to Accept, Accept with Contingencies, Reject, or Request more information. The activity screen also contains a section for the user to make comments and upload additional documents |

### 8.1 GHS Internal Procedure for HSSC Co-operative Review

Once steps under 7.0 have been completed and the information submitted to the GHS IRB office, the following procedures will be followed:

1. GHS OHRP Medical Director and/or IRB Chair(s) will decide whether to accept the lead institution’s IRB approval without change, or schedule the study for full IRB committee review.

2. If full committee review is required the information will be given to IRB members for their review prior to the meeting.

3. The GHS IRB may make administrative changes to the consent document (i.e. addendum “GHS Addendum to (lead institutions name) study (study title)” to the consent form) to reflect local requirements. These changes will be communicated to the PI who is responsible for informing the lead IRB of the changes. The GHS IRB may also conduct its own independent review.

4. If an independent review is conducted the GHS IRB coordinator will communicate to the PI responsible for informing the lead IRB of approval and/or changes.
9.0 ASSURANCE

As an institution involved in research conducted or supported by the federal government, GHS must submit assurances to the OHRP that include a statement of principles and guidelines that governs the institution, its faculty and staff, in the discharge of its responsibilities for protecting the rights and welfare of human subjects taking part in research conducted at, or sponsored by, the institution, regardless of the source of funding.

The Assurance shall include written procedures which the IRB(s) will follow for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator, for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate immediate hazards to the subject.

The IRB shall have written procedures ensuring prompt reporting to the IRB, appropriate GHS administrators, and appropriate governmental officials of any unanticipated problems involving risks to subjects, and ensuring prompt reporting to the appropriate institutional officials of any serious or continuing noncompliance with the Policies and Procedures of the IRB or any suspension or termination of the IRB approval. 21 CFR 56.108 and 45 CFR 46.103

A copy of the Greenville Health System’s Federal Wide Assurance (FWA) will be maintained in the office of the Medical Director, Office of Human Research Protection (OHRP) and will be available to the GHS community via the GHS OHRP website.

10.0 CONCERNS OR SUGGESTIONS REGARDING THE GHS IRB AND THE HRPP

Investigators may address concerns and/or suggestions about either the IRB or the HRPP by submitting a written document to the Institutional Official.

Investigators with concerns or complaints about the service they have received from the GHS OHRP, or one of the IRBs, and are unable to resolve the problem after direct communication with the GHS OHRP Medical Director, or the IRB, may submit their concerns and/or suggestions, in writing, to:

GHS Institutional Official
Health Science Administration Building
701 Grove Road
Greenville, S.C. 29695

The Institutional Official may respond verbally, or in writing, and take any action necessary to address the concerns and/or suggestions.
1.0 MEMBERSHIP

The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such subjects as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competency necessary to review specific research activities, the IRB should be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice 21 CFR 56.107(a) and 45 CFR 46.107(a). The IRB may, at its discretion, invite individuals with competence in special areas to assist in the review of complex issues, which requires expertise beyond or in addition to that available on the IRB.

Appointments to the IRB will be recommended by the Medical Director of the GHS Office of Human Research Protection (OHRP), in consultation with the Chairperson and/or selective members of the relevant IRB, to the designated Institutional Official. The Institutional Official will subsequently notify the appropriate committee and applicable process as recommended by the GHS Board of Trustees.

The Institutional Official reviews the performance of the IRB Chair at least annually and provides feedback to the Chair. The Institutional Official may seek input from the IRB members, investigators and the IRB administrative staff.

The IRB Chair will review the performance of the IRB members at least annually and provide feedback to the members. The IRB Chair may consider attendance, participation during the meeting(s), preparedness and knowledge in evaluating the membership.

Completion of the GHS anonymous IRB Member survey is also encouraged in order to better serve the needs of the IRB members.

Each committee shall be composed of at least 5 members. Members shall be appointed for a term of three (3) years by the GHS Board of Trustees. There are no term limits for membership. Members shall serve until they resign or are replaced by the GHS Institutional Official. The Institutional Official will subsequently notify the GHS Board of Trustees of any IRB membership and/or leadership changes. At a minimum, the membership shall be composed of one physician, one nonscientist and one person not affiliated with the institution, and the IRB shall have sufficient expertise and diversity to evaluate ethical issues involved in protocols that are sent for IRB review.
When needed, individuals with similar backgrounds and training may serve as an alternate for another individual. For example, one community member may serve as an alternate for another community member, one clergy representative may serve as an alternate for another clergy representative. In addition, when needed, a committee may have representatives from other institutions as voting members when that committee reviews research for other institutions.

Other committee requirements:

- No IRB has members who are all males or all females.
- No IRB has members who represent a single profession.
- Each IRB has at least one member whose primary concerns are in scientific areas.
- Each IRB had at least one member whose primary concerns are in nonscientific areas.
- Each IRB has at least one member who is not otherwise affiliated with the organization and who is not part of the immediate family of a person who is affiliated with the organization.
- Each IRB has at least one member who represents the perspective of research subjects.

Individuals who are responsible for business development are prohibited from:

- Serving as members or ex-officio members on the IRB.
- Carrying out day-to-day operations of the review process.

A list of IRB members is submitted to the Office for Human Research Protections in the GHS IRB Registration. This list will include each member identified by name; earned degrees; representative capacity; scientific or nonscientific status of each member; their affiliation status (a member is affiliated if a family member is an employee of the organization); indications of experience sufficient to describe each IRB member’s chief anticipated contributions; and employment or other relationship to the institution. Alternate members will also be included with the primary members or class of primary members for whom each alternate member can substitute.

It is the policy of the Greenville Health System not to release the names of the members of the IRB, except as required by law or regulation.

2.0 IRB MEMBER DUTIES AND RESPONSIBILITIES

GHS IRB members are responsible for ensuring investigators (and their research) protects the rights and welfare of research participants by reviewing and approving human research in a manner consistent with federal regulations, state and local laws, and institutional guidelines and policies.

The IRB members will:

- Ensure the investigators use procedures which are consistent with sound research design and which do not expose subjects to risks, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- Determine that risks to the subjects are reasonable in relation to the anticipated benefits to subjects, if any, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB member should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB member should not consider possible long-range effects of applying knowledge gained in the research.
- Determine that selection of subjects is equitable.

In making this assessment, IRB members should consider the following:

- The purpose(s) of the research and the setting in which it is conducted; and
Whether there are special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, cognitively or mentally impaired persons, or economically or educationally disadvantaged persons.

Determine whether the informed consent is adequate, and if not, request clarifications and changes in the consent form to adequately explain the purpose of the research, the risks and benefits entailed therein, and that it contains all other federally or locally mandated elements.

Determine that the research plan makes adequate provision for monitoring the data collected to ensure the safety of the subjects.

Determine that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data.

Ensure additional safeguards are in place to protect the rights and welfare of subjects that are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, cognitively or mentally impaired persons, or economically or educationally disadvantaged persons.

Before the IRB meeting, the IRB should:

- Review the assigned projects to be presented.
- Get any questions answered before the IRB meeting.
- Discuss any questions about the assigned projects with the investigator, other IRB members, or consultants prior to the IRB meeting.
- Decide whether you feel the investigator should attend the meeting to discuss any problems or concerns noted with the project.
- If specific changes are needed in the consent form, come to the meeting with recommended wording to be transmitted to the investigator.

3.0 ATTENDANCE REQUIREMENTS

Members are expected to attend their respective meetings, where attendance is noted for the minutes. Attendance of each IRB member will be reviewed annually on a calendar year basis by the Medical Director of the GHS Office of Human Research Protection (OHRP), and the appropriate committee chairperson(s). Any member who has missed more than one-half of the year’s meetings will be counseled by the GHS OHRP Medical Director, and the appropriate committee chairperson(s), about the coming year’s meetings. If the Medical Director, and the appropriate committee chairperson(s), feels that the member in question will be unable to attend the majority of the next year’s meetings, he/she will recommend to the Institutional Official immediate replacement of the member.

Prospective members will serve a 3-month, non-voting, orientation with the proposed committee. Upon successful completion, the prospective member will be eligible for the initial appointment process.
4.0 ALTERNATE MEMBERS
Certain members may be designated alternate members, as submitted to the Office for Human Research Protections in the IRB Registration. An alternate member may only substitute for his/her designated member if that member is not available to vote (e.g. absent, recused for conflict of interest). If more than one alternate member is present at a meeting where the member is not present, only one alternate may vote. Alternate members have the same rights and responsibilities as the primary members when the alternate member represents a primary member.

4.1 IRB Consultants
At the time of preliminary review of a new project application or modification, the IRB chair or primary reviewer may determine that the study requires further review by a consultant with expertise outside of the current IRB membership. This determination may be made based on the study, specific privacy and confidentiality concerns, or considerations relative to a particular study population.

Upon identifying the need for a consultant review, the chair and/or primary reviewer, in consultation with the chair, will identify a consultant with appropriate expertise and experience based on the particular issues to be addressed. Consultants are identified by the chair of the IRB based on the type of review required and/or expertise in the discipline of the submission. For issues requiring only simple clarification, a written set of questions will be developed for submission to the consultant. The consultant’s written response to these questions will be provided to the full IRB for review at the time of the convened meeting. For issues requiring more than simple clarification, the consultant may also be invited to attend the full board meeting during the review of that particular study. The consultant will leave prior to the final vote by the IRB. Documentation of the discussion with the consultant will be included in the meeting minutes and the protocol review files.

No person with a conflict of interest will serve as a consultant for the purposes described in this section. Any individual asked to participate, as a consultant, will be required to sign a confidentiality agreement and declare in writing that they have no conflicts of interest involving the study for each consultation.

5.0 IRB MEMBER REMOVAL/VACANCY
IRB members may be removed and new members appointed by the Institutional Official, acting on behalf of the GHS Board of Trustees. The Institutional Official will subsequently notify the GHS Board of Trustees of any IRB membership and/or leadership changes.

6.0 IRB CHAIRPERSON(S) APPOINTMENT
The Chairperson(s) of the IRB will be recommended by the Medical Director of the GHS Office of Human Research Protection (OHRP), in consultation with the Designated Institutional Official to the GHS Board of Trustees for approval. The Chairperson’s names and credentials are submitted to the Office of Human Research Protections in the IRB Registration. The Chairperson(s) shall be a licensed physician. Upon the above recommendation of the OHRP Medical Director and the GHS Institutional Official, the GHS Board of Trustees will appoint the IRB Chair.
6.1 Length of Term

Term of office for the Chairperson(s) shall be 3 years. The Chairperson shall serve until a successor is appointed. The IRB Chairperson may be re-approved as outlined in this document.

6.2 Duties

- The Chairperson(s) shall direct the meetings in accordance with institutional and federal requirements, as well as parliamentary procedures from Robert’s Rules of Order. This includes keeping the discussion focused on important IRB issues and seeing that the full-committee meeting process is both efficient and effective.
- The Chairperson(s) should have an in-depth understanding of the ethical issues, state law, institutional policy, and federal research regulations that are applicable to studies that are reviewed by the IRB.
- The Chairperson(s) is the principal signatory official for the IRB correspondence but may designate as appropriate, the Vice-Chairperson, IRB Director, the IRB Administrator, and any designated IRB members to review selected IRB documents and materials.
- The Chairperson(s) should play a leadership role in establishing and implementing IRB policy.
- The Chairperson(s) should review all protocols presented to the full-committee. The IRB Chairperson(s) is expected to have read each full-committee protocol and to communicate with any other reviewers so that important IRB issues are resolved or identified before the full-committee meeting (i.e. the IRB Chair is formally listed as the primary or secondary reviewer for all full-committee protocols).
- The Chairperson(s) should coordinate with the IRB administration in the drafting of letters from the IRB to researchers regarding IRB decisions.
- The Chairperson(s) should serve as reviewer for research that is reviewed by an expedited process. This task can be shared with other members of the IRB, depending on expertise.
- The Chairperson(s) should represent the IRB in defending or discussing IRB decisions with researchers.
- The Chairperson(s) will review the performance of IRB members on an annual basis and provide feedback.

7.0 CHAIRPERSON(S) REMOVAL/VACANCY

The IRB chairperson(s) may be removed and a new chairperson(s) appointed by the Institutional Official, acting on behalf of the GHS Board of Trustees. The Institutional Official will subsequently notify the GHS Board of Trustees of any IRB membership and/or leadership changes.

8.0 VICE-CHAIRPERSON(S) IRB APPOINTMENT

The Vice-Chairperson(s) of the IRB will be recommended by the Medical Director of the GHS Office of Human Research Protection (OHRP), in consultation with the Designated Institutional Official to the GHS Board of Trustees for approval. The Vice-Chairperson’s names and credentials are submitted to the Office of Human Research Protections in the IRB Registration. The Vice-Chairperson(s) shall be a licensed physician. Upon the above recommendation of the OHRP Medical Director and the GHS Institutional Official, the GHS Board of Trustees will appoint the IRB Chair.
8.1 **Length of Term**
Term of office for the Vice-Chairperson shall be 3 years. The Vice-Chairperson shall serve until a successor is appointed. The IRB Vice-Chairperson may be re-approved as outlined in this document.

8.2 **Duties**
In the absence of the Chairperson, or as delegated by the Chairperson, the Vice-Chairperson shares the same functions and duties as the Chairperson.

9.0 **VICE-CHAIRPERSON(S) REMOVAL/VACANCY**
The Vice-Chairperson(s) may be removed and a new vice-chairperson(s) appointed by the Institutional Official, acting on behalf of the GHS Board of Trustees. The Institutional Official will subsequently notify the GHS Board of Trustees of any IRB membership and/or leadership changes.

10.0 **IRB MEMBER(S) ORIENTATION, EDUCATION AND TRAINING**

10.1 **Orientation**
The Medical Director, along with the appropriate Chairperson(s), shall provide new members with the GHS ORHP IRB Policy and Procedures Manual, and all applicable federal and state regulations.

10.2 **Education and Training**
Members shall be required to complete the Collaborative IRB Training Initiative (CITI) program for biomedical research and for IRB members. Members will also be required to complete the CITI refresher course every three (3) years.

10.3 **Continuing Education and Training**
All members shall receive copies of various IRB-related publications (e.g. *Report on Human Research Compliance*) and new updated guidance documents from the FDA, OHRP, or other governing agencies.

11.0 **UNDUE INFLUENCE**
Any IRB member with concerns about undue influence or coercion (e.g., someone outside of the IRB seeks to influence the outcome of the IRB review) should report these concerns to the GHS OHRP Medical Director, OHRP Director, IRB Chair, and/or the Institutional Official. If the concern is related to the GHS OHRP Medical Director, OHRP Director, IRB Chair, or Institutional Official, the GHS General Counsel should receive the report. Individuals may also report concerns to the GHS General Counsel anonymously.

Any IRB staff (e.g., IRB Coordinator) with concerns about undue influence or coercion (e.g., someone outside of the IRB seeks to influence the outcome of the IRB review) should report these concerns to the GHS OHRP Medical Director, OHRP Director, IRB Chair, and/or the Institutional Official. If the concern is related to the GHS OHRP Medical Director, OHRP Director, IRB Chair, or Institutional Official, the GHS General Counsel should receive the report. Individuals may also report concerns to the GHS General Counsel anonymously.
OHRPP leadership (including, but not limited to the OHRP Medical Director, OHRP Director, Institutional Official, IRB Chair, or IRB Coordinator) concerned about undue influence or coercion (e.g., someone outside of the IRB seeks to influence the outcome of the IRB review) should report this concern to the GHS General Counsel. Individuals may also report concerns to the GHS general Counsel anonymously.

Concerns regarding undue influence or coercion shall be documented by the report recipient. Appropriate GHS Officials, including the Institutional Official, the GHS General Counsel, or their designees will promptly investigate any concerns, and report their findings to the appropriate Institutional Official, IRB Medical Director, and/or other Organizational Officials. Leadership will act immediately, as necessary, to remedy any concerns or execute remedial actions, per investigation findings.
1.0 SCOPE

Federal regulations prohibit a member of the IRB from participating in the initial or continuing review of any project in which the member has a “conflicting interest,” except to provide information at the IRB’s request. 45 CFR 46.107(e)

Any IRB member with a conflicting interest in a project must disclose that to the IRB and if the vote of the IRB impacts the financial interest to the member disclosing the conflict, then the member must leave the room during the discussion of the project and the related vote, except if the member is providing information at the IRB’s request. IRB members and consultants with a conflict of interest are not counted towards quorum. The meeting minutes will document the recusal (i.e. the temporary absence of the IRB member during the deliberation and vote on the project with respect to which the member has a conflict).

In the case of expedited IRB review (outside of a convened meeting, by a designated reviewer), the reviewer should disclose any conflicting interest in a project in advance to the IRB Office and should not review the project.

2.0 TO WHOM DOES THIS POLICY APPLY?

It applies to all members of the GHS IRB and to ad hoc reviewers, who are not IRB members but sometimes are asked to review a project because of their expertise (collectively, “IRB members” or “members”). This also includes conflicting interest of immediate family members (spouse, dependent children).

This policy covers each type of IRB review including unanticipated problems involving risks to participants or others, or non-compliance with regulations or laws or the requirements of the IRB.

3.0 WHAT IS A “CONFLICT OF INTEREST”?

Generally, a conflicting interest includes (1) participation in the project; (2) a financial interest as defined below; and/or (3) any other examples referenced below. A conflict may arise because of an interest in the IRB member or his/her family; the aggregate interest of the IRB member and family is considered.

**Participation in the project:** For purposes of this policy, generally means the member is listed on the protocol/project, or will be included (or reasonably may be expected under academic standards to
be included) as a co-author on a publication of the project’s results or the IRB member, consultant, or their immediate family is involved in the design, conduct, or reporting of the research.

**Participation in the project excludes** serving as a member of the IRB or the data monitoring board overseeing the project.

**Financial Interest Related to the Research** is defined as financial interest in the sponsor, product or service being tested. Financial interest of the member or a member of the investigators immediate family (spouse, dependent children) may be defined as situations in which the value of compensation could be affected by study outcome; a proprietary interest in the tested product, including, but not limited to, a patent, trademark, copyright or licensing agreement; any equity interest in the sponsor of a covered study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices; any arrangement where the value of the ownership interest would be affected by the outcome of the research or ownership interest exceeds 5% interest in any one single entity when aggregated for the immediate family. This requirement applies to all covered studies, whether ongoing or completed; any equity interest in a publicly held company that exceeds $10,000 in value. The requirement applies to interests held during the time the member is carrying out the study and for 1 year following completion of the study; and significant payments of other sorts, which are payments that have a cumulative monetary value of $10,000 or more made by the sponsor of a covered study to the member or the member’s institution to support activities of the investigator exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the member is carrying out the study and for 1 year following completion of the study.

4.0 **Other Examples of Conflicting Interest Include But Are Not Limited To:**

- serving as a Board member (of a Board of Directors or scientific advisory board) or as an executive to a Business that is supporting or facilitating the project, or that owns or has license rights to the Technology the project is on:
- having certain non-financial interests that may raise a real or perceived conflict. These will depend on the circumstances. They may include, for example, having direct supervision over the investigator conducting the project, or participating in a separate project on Technology that may directly compete with the Technology in the project under review.
- for clarification: (i) a department chairperson ordinarily does not have a conflict simply by virtue of that position; a conflict could arise, though, if the chairperson had a closer, direct supervisory relationship over a department researcher; (ii) if a junior person in an IRB member’s research group submits a protocol, the IRB member has a conflict and cannot review the protocol.
- any real or perceived conflict, or a concern that there may be a real or perceived conflict, that is not addressed above should be raised with the IRB Chairperson. If the IRB Chairperson determines there is a conflicting interest, then the member shall recuse himself or herself. The IRB Chairperson reserves the right to request recusal as appropriate in any particular circumstance.

5.0 **HOW AND WHEN SHOULD AN IRB MEMBER DISCLOSE A POTENTIAL CONFLICTING INTEREST**

When IRB members review materials before a meeting, they should review the list of projects for initial or continuing review with this issue of conflicts in mind and should disclose any potential issue
to the Chairperson in advance of the meeting when possible. At the beginning of each IRB meeting, members also will be reminded of the conflicts policy and should disclose any potential conflict at that time.

A designated IRB reviewer performing expedited review of projects similarly should review the list of projects and disclose any potential issue in advance to the IRB Office.

Ad hoc reviewers will receive a copy of this policy with materials for the project they are reviewing.

6.0 OTHER ISSUES THAT SHOULD BE CONSIDERED

Senior positions of responsibility: It is expected that individuals with greater responsibilities for reviewing human subjects research may have potentially more influence over the review and approval of a project and thus should be particularly sensitive to any perceived or real conflicting interest. Accordingly, the IRB Chairpersons and research administrators or institutional officials with research oversight authority who are involved in reviewing a project or projects should disclose any potential conflicting interest to the appropriate supervisor; such disclosure may require additional institutional review.

GHS projects: An IRB member may not consult for a Business to assist in shepherding a project through the IRB process when the project will be performed within the GHS.
The Greenville Health System
Office of Human Research Protection
HRPP Policies and Procedures

**Title: IRB Meetings**

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1.0 **LOCATION**

IRB meetings will be held in a suitable conference room at Greenville Health System. A schedule for the dates and locations of meetings is available through the IRB office. Scheduled meetings may be cancelled or rescheduled for holidays, a lack of quorum, or inclement weather. Meetings are cancelled or rescheduled by the action of the Chairperson(s) in conjunction with the Director of the Office of the IRB.

2.0 **SCHEDULING OF THE MEETINGS**

Each committee shall hold regularly scheduled meetings. These meetings are held once a month. In addition, a special meeting may be called by the Chairperson(s) or three other committee members, to review projects or conduct such other business as may be necessary. Material relevant to the agenda at each meeting will be made available to each IRB member at least one (1) week prior to each IRB meeting.

2.1 **Primary Reviewer**

A primary reviewer is assigned in advance of a full board meeting. The chair may, at his/her discretion, serve as the primary reviewer. In selecting the primary reviewer, consideration is given to the individual’s knowledge of the subject area embodied in the proposal. If no IRB member has adequate knowledge or experience to review a given protocol, the IRB chair will engage a consultant with appropriate expertise and experience to conduct the review.

The primary reviewer conducts in-depth review of all items required for IRB submission of a new application (see HRPP Policy No. 12.0 Research Protocols) including the Informed Consent Document(s), and all supplemental materials (including, if applicable, the grant application, protocol, and investigator’s brochure). For initial review of research by a convened IRB, at least one member (the primary reviewer) is provided and reviews both the (a) DHHA-approved sample consent document (when one exists) and (b) complete DHHS-approved protocol (when one exists).

The primary reviewer is strongly encouraged to contact the investigator in advance of the board meeting for additional information or clarification. The primary reviewer leads the discussion of the new project or continuing review application. The primary reviewer may not have a conflict of interest regarding the project under review and must notify the chair of any conflict.
Primary reviewers are provided an initial review checklist to ensure that all criteria for approval of research have been fulfilled. Although the checklists are used as an education tool and completion of the checklists are not mandatory, the IRB strongly encourages the primary reviewer to complete and return the checklist to the IRB coordinator to assist in documenting minutes and electronic communications with the investigator.

If the primary reviewer is unable to attend the regular scheduled meeting, it is their responsibility to notify the IRB office as soon as possible so that the IRB coordinator can appoint a new primary reviewer in time to present at the meeting.

2.2 **Consultants**

At the time of preliminary review of a new project application or modification, the IRB chair or primary reviewer may determine that the study requires further review by a consultant with expertise outside of the current IRB membership. This determination may be made based on the specific design of the study, the ethical issues of the study, the potential risks or benefits of the study, specific privacy and confidentiality concerns, or considerations relative to a particular study population.

Upon identifying the need for a consultant review, the chair and/or primary reviewer, in consultation with the chair, will identify a consultant with appropriate expertise and experience based on the particular issues to be addressed. Consultants are identified by the chair of the IRB based on the type of review required and/or the expertise in the discipline of the submission. For issues requiring only simple clarification, a written set of questions will be developed for submission to the consultant. The consultant’s written response of these questions will be provided to the full IRB for review at the time of the convened meeting. For issues requiring more than simple clarification, the consultant may also be invited to attend the full board meeting during the review of that particular study. The consultant will leave prior to the final vote by the IRB. Documentation of the discussion with the consultant will be included in the meeting minutes and the protocol review files.

No person with a conflict of interest will serve as a consultant for the purposes described in this section. Any individual asked to participate, as a consultant, will be required to sign a confidentiality agreement and declare in writing that they have no conflicts of interest involving the study for each consultation.

3.0 **VISITORS**

Visitors are allowed to attend IRB meetings with permission of the Chairperson(s). Visitors may request permission to attend IRB meetings by contacting the Office of Human Research Protection. Visitors must agree to sign a statement of confidentiality prior to attending any IRB meeting and may not remove any written materials from the room that are distributed during the meeting (agendas, minutes, study protocols) with the exception of educational materials. If the Chair(s) moves the meeting to Executive Session then all visitors will be asked to leave the room until the Executive Session has ended.

4.0 **QUORUM/VOTING PROCEDURES**

After discussion, the IRB members vote their decision, which can include approval, conditional approval (conditions that require simple concurrence), deferral, and disapproval. Voters (for, against, abstain), those recused, and the attendance are recorded in the minutes. The IRB observes the following regulations in its voting:
A quorum, as defined in the GHS OHRP Policy No. 3.0, is required to transact business.
- Quorum is determined to be met by the Chair and is documented on the attendance sheet and in the meeting minutes.
- A majority vote of the members present is needed to approve or disapprove the study.
- Full voting rights of all members (each member has one vote and if the member is unable to vote (absent or recused), then one designated alternate member may vote in place of the member). Ex-officio members are non-voting members.
- The designated IRB coordinator is a non-voting member.
- All IRB members are provided laptops to view meeting materials. The meeting materials are also projected onto a screen or printed as handouts.
- IRB business may be conducted by telephone or video conferencing as long as the IRB member(s) receives and has the opportunity to review the material prior to a determination on a given protocol and can participate in the discussion that occurs in real-time with the majority of the IRB members. Such members are counted as part of the quorum and may vote.
- Prohibition against conflict of interest - voting members who have a conflict of interest may be present to answer questions about the protocol but then must leave the room and recuse themselves from deliberations and voting. The presence of a conflict and the recusal are recorded in the minutes.
- A member can abstain and quorum will not be lost; however, if there is a conflict of interest and the member abstains then quorum will be lost.
- At convened IRB meetings:
  - If the quorum is lost during a meeting, the IRB cannot take votes until the quorum is restored.
  - If required members (e.g. non-scientific) leave the room and quorum is lost votes cannot be taken until the quorum is restored, even if half of the members are still present.
- At least one member who represents unaffiliated membership (i.e. community members) is present at convened meetings.
  - This may be accomplished by one of the following:
    - Requiring the members as part of the quorum.
    - Placing an attendance requirement on the member (e.g. attend 10 of 12 meetings per year).
- At least one member who represents the general perspective of subjects is present at convened meetings.
  - This may be accomplished by one of the following:
    - Requiring the members as part of the quorum.
    - Placing an attendance requirement on the member (e.g. attend 10 of 12 meetings per year).
- The chair and vice chair typically attend all IRB meetings and are eligible to vote.
- Prior to each meeting, the chair and/or vice chair works with the IRB coordinator to review the meeting agenda and studies to be discussed. The chair serves as the meeting facilitator and works with the IRB coordinator to provide any necessary post meeting follow-up with the investigators.
- If the IRB reviews research that is involving categories of participants vulnerable to coercion or undue influence, one or more individuals who are knowledgeable about or experienced in working with such participants are present.

(Note that the unaffiliated member, the member representing the general perspective of subjects, and the non-scientific member may be the same person or they may be represented by two or three different persons.)
5.0 APPROVAL PERIOD AND EXPIRATION OF IRB APPROVAL

The IRB will determine the period of approval at the time a protocol receives approval. The approval period for research is based on the date of the convened meeting at which the IRB approved the protocol or approved the protocol with modifications. An IRB approval period expires on the last date that the protocol was approved. For example, a protocol approved on July 1st for one year will expire on June 30th at the end of the business day.

6.0 MEDICAL DIRECTOR

The GHS OHRP Medical Director may serve as a full voting member of all the IRBs as well as any other relevant sub-committee.

7.0 MINUTES AND AGENDA

Meeting agendas and minutes are prepared for each convened IRB meeting. Each IRB reviews and approves the minutes of its previous meetings during subsequent convened IRB meetings.

The GHS IRB minutes document separately deliberations, actions, and votes for each protocol reviewed by the convened committee. Additionally, education materials distributed, audits discussed and protocol deviations submitted are also noted in the minutes. All IRB minutes are confidential.

Minutes contain, at a minimum:
1. The date, time and location of the meeting;
2. Documentation of voting and non-voting members present, absent, and excused and any alternate members replacing absent or excused members;
3. When a member leaves the meeting, and/or any loss of quorum, the names of IRB member(s) who left the meeting because of a conflicting interest along with the fact that a conflicting interest is the reason for the absence;
4. Attendance of staff, members and guests;
5. Educational material distributed;
6. Actions taken by the IRB at the meeting on any of the following;
   a. Initial reviews and the approval period;
   b. Continuing reviews and the approval period;
   c. Amendments;
   d. Serious adverse events;
   e. Resubmitted protocols;
   f. Safety or investigational brochure updates;
   g. Expedited reviews of protocols;
   h. Final approvals for protocols conditionally approved at previous meetings;
   i. Protocol deviations;
   j. Any non-compliance issues;
7. Separate deliberations for each action and all votes on actions, including number of members voting for, against, those recusing themselves from voting (and discussion) and those abstaining from voting on actions;
8. Administrative issues;
9. A written summary of discussion of issues pertaining to protocol reviews, particularly controverted (disagreement over) issues and their resolution;
10. The basis for requiring changes in or disapproval of research, and any subsequent resolution of those requirements or disapproval;
11. Any determinations regarding waiver of the requirement for informed consent, for informed consent documentation, or for particular elements of informed consent;
12. Justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document;
13. Unless documented in the IRB records determinations required by the regulations and protocol-specific findings justifying those determinations for:
   ▪ Waiver or alteration
   ▪ Research involving pregnant women, fetuses, and neonates
   ▪ Research involving prisoners
   ▪ Research involving children
14. The results and issues pertaining to audits of research conducted by the IRB.
15. The rationale for significant risk/non-significant risk device determinations.

**8.0 NOTIFICATION OF IRB ACTIONS TO THE INSTITUTIONAL OFFICIAL**

The GHS OHRP office staff is responsible for sending copies of the minutes of each IRB committee meeting to the Institutional Official or designee.
9.0 COMMUNICATION WITH INVESTIGATORS CONVEYING THE OUTCOME OF IRB MEETINGS

IRB actions that occur during IRB meetings are promptly conveyed to the Principal Investigator in writing. Communications include conditional approval and its conditions, or deferral or disapproval including the reasons for non-approval. Letters and minutes may suggest changes to the protocol and/or consent form that are required before the protocol will be reconsidered by the committee. An IRB member may volunteer or may be assigned to work with the Principal Investigator to address the IRB concerns.

9.1 Revisions Prior to Final Approval

Revisions to new and continuing human subjects applications may be required. Correspondence is sent to the investigator detailing requests for revisions, clarification, or additional information as well as information regarding continuing review. The investigator has 60 days to respond to the revisions requested. If the investigator does not respond in 60 days, the application is deactivated and returned. If the investigator wishes to conduct a study that has been deactivated, the investigator must submit a new application, incorporating comments from the prior IRB review.

When specific changes are requested in the protocol and/or continuing review document(s), these are reviewed for compliance before final approval is given.

- If the changes are minor and require only simple concurrence, the final review and approval may be provided by the chair or designee.
- Instances where extensive/general revisions are requested during a full board review that require more than simple concurrence, the revised documents must be returned to the full board for its review and approval.
  - Examples of changes that must be reviewed by the full board include wording such as describe, justify, explain, expand on, or provide.

The application receives final approval when all required changes have been submitted, reviewed and approved.

When the IRB specifies condition(s) for approval of a protocol that are to be verified by the IRB Chair or designee, continuing review must occur no more than one year from the date of review at the convened meeting.

When the IRB is reviewing modifications to previously approved research, if the IRB specifies condition(s) for approval that have 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.

Upon receipt of final approval, the GHS IRB staff stamps approved Informed Consent Document(s), HIPAA authorizations and other materials (e.g. letters to subjects, ads) with the IRB approval stamp, the date of approval, and the date of expiration. These documents are sent to the principal investigator along with the final approval letter that includes information on the date of human subjects research expiration of approval. The letter reminds an investigator that changes in research activity may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to subjects.
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**SCOPE**

1. The IRB shall be responsible for reviewing all research projects submitted by GHS or its medical staff and relying institutions or their medical staff and the IRB must approve all projects before being initiated. GHS, through the IRB, ensures that research involving human participants does not commence until research has received all approvals required by the Greenville Health System. IRB executes this charge via periodic meetings with IRB leadership (e.g., OHRP Medical Director, OHRP Director, GHS’ Institutional Official) and GHS department chairs, academic vice chairs or designees. Periodic meetings include survey of scholarly activity and stakeholder re-education pertaining to research definition(s) (see HRPP Policy No. 3.0) and investigator/principal investigator responsibilities (see HRPP Policy No. 10.0). IRB leadership may also utilize committee meetings (e.g., Academic Council, Research Division Advisory Council) to re-educate GHS stakeholders on requisite processes.

2. The IRB shall try to ascertain, insofar as possible, risks to any subject involved in a research study. For approval, the sum of the benefits to the patient and knowledge to be gained should be expected to outweigh such risks.

3. Except for research described in the Policies and Procedures entitled “Emergency Use of a Test Article”, and except for research with limited involvement of human subjects as described in 45 CFR 46.101(b) or with criteria described in 45 CFR 46.116(d), the IRB shall require that a committee approved consent form be utilized in each project.

4. The IRB shall require that an active member of the GHS medical staff or a member of the GHS professional staff, at the discretion of the committee, is responsible for and directly involved with all GHS related projects. Exception being those studies approved for another institution. In those cases, a member of that institution’s medical staff or professional staff must be responsible for those projects.

5. Projects which involve research on deceased individuals must be reviewed by the IRB. Research involving decedents is not regulated under the Common Rule (45 CFR 46)” however, if you or a member of the study team will be accessing Protected Health Information (PHI) of the decedent(s), the project must comply with HIPAA Privacy Protections. In order to obtain a HIPAA Waiver of Authorization the IRB Chairperson, or his/her designee, will evaluate the application to ensure that the use and/or disclosure of PHI for the project involves no more than minimal risk to the privacy of the individual(s). In making this determination, the IRB Chairperson, or his/her designee, will consider the following: (1) the use of disclosure being sought is solely for research on the PHI of decedents; (2) the PHI being sought is necessary for the research; (3) at the request of the covered
entity, the researcher will be able to provide documentation of the death of the individuals about whom information is being sought.

6. The IRB shall evaluate all ongoing projects at least annually. More frequent evaluation may be required at the discretion of the committee through consideration of the presumed degree of research risks.

7. The IRB shall require that all projects conducted at GHS are compatible with the mission of the GHS.

8. The IRB shall review all project summaries after completion.

9. The IRB shall assure that investigators provide at least the following information:
   - Professional qualifications to do research
   - Completed application form
   - Complete protocol to include:
     a. Title of the study
     b. Purpose of the study
     c. Summary of results related research
     d. Subject selection criteria, including any tests required for participation
     e. Subject exclusion criteria
     f. Study design
     g. Description of procedures to be performed
     h. Expected side effects
     i. Provision for managing adverse reactions
     j. Evaluation schedule and length of study
     k. Investigator’s brochures for investigational drugs and/or package inserts for approved drugs
     l. Appropriate consent form (please refer to Policies and Procedures entitled “Informed Consent”)

10. The IRB shall report its findings and decisions in a timely manner to the investigator, appropriate GHS administrators, and appropriate governmental officials.

2.0 DETERMINATION OF WHETHER RESEARCH IS HUMAN PARTICIPANT RESEARCH

Completion of the eIRB SmartForm application and its questions concerning whether the project will result in the development of generalizable knowledge or will obtain data about living individuals will determine whether the project constitutes research involving human participants. Final determination about whether IRB review will be required rests with the GHS IRB using criteria under federal regulations 45 CFR 46.102.

Research investigators will be notified of the determination by letter from eIRB or the IRB Committee Chair.

DETERMINATION OF WHETHER RESEARCH IS COMMUNITY BASED PARTICIPATORY RESEARCH (CBPR)

Community-Based Participatory Research (CBPR) is a partnership approach to research (see “research” in HRPP Policy no. 3.0) that equitably involves, for example, community members, organizational representatives, and researchers in all aspects of the research process, in which all partners contribute expertise and share decision making and responsibilities. As such, community members participating in this research must evidence the same ethics training required of any
investigator included on a study application (see HRPP Policy No. 10.0, Sect. 2.1). Principal investigators of CBPR are required to be members of the GHS medical professional staff, nursing staff, employees of GHS, or a faculty member of a GHS-affiliated institution if proposed CBPR collects or reviews patient data. All other investigator requirements additionally apply (e.g., HRPP Policy No.10.0, Sect. 1.0).

OHRP will periodically educate committee members on CBPR tenets to ensure IRB committee member competence in reviewing CBPR. Education may occur in academic forum (e.g., Research Division Advisory Group meetings) or via individual remediation.

The IRB Chair is authorized to solicit an IRB consultant to determine whether the proposed work qualifies as CBPR (see HRPP Policy No. 5.0, Sect. 4.1; HRPP Policy No. 7.0, Sect. 2.1). For these purposes, a consultant may be a representative of the study population; the consultant may also evidence an academic or professional background germane to CBPR, including, but not limited to: Public Health, Sociology, Public Policy, Regional Planning, or Social Welfare. The IRB Chair may additionally solicit either the unaffiliated committee member (see HRPP Policy No. 5.0, Sect. 1.0) or the designated consultant to serve as the primary study reviewer for CBPR, particularly when such proposals include or impact special populations exemplified in HRPP Policy No. 36.0. This CBPR-specific policy does not encroach upon established quorum/voting procedures outlined in HRPP Policy No 7.0, Sect. 4.0.

**DETERMINATION OF WHETHER RESEARCH IS PATIENT-CENTERED OUTCOMES RESEARCH (PCOR)**

Patient-Centered Outcomes Research (PCOR) is comparative effectiveness research explicitly and intentionally informed by patients’ stated perspectives on intervention value (e.g., potential outcome per cost), and preferences/priorities, per the intervention’s: benefits, harms, or alternatives. PCOR gleans these insights via patient engagement, defined as meaningful involvement of patients, caregivers, clinicians, and other healthcare stakeholders throughout the research process—from topic selection through design and conduct of research to dissemination of results. OHRP decides who can perform any research study involving human subjects at GHS: principal investigators of PCOR are required to be members of the GHS medical professional staff, nursing staff, employees of GHS, or a faculty member of a GHS-affiliated institution. (HRPP Policy No. 10.0, Sect. 1.0). All investigator requirements apply (e.g., HRPP Policy No. 10.0, Sect. 1.0 and Sect. 2.1). Further, any stakeholder (e.g., patient or caregiver) participating in “the conduct of research” must be OHRP-approved, and evidence the same ethics training required of any investigator included on a study application (see HRPP Policy No. 10.0, Sect. 2.1). “Conduct of research” includes, but is not limited to: soliciting or reviewing informed consent (HRPP Policy No. 13.0), requesting, accessing or reviewing patient data (HRPP Policy No 32.0).

Study team members prohibited from serving as investigators, per HRPP Policy No. 10.0, Sect 1.0 and Sect 2.1 (e.g., patients, caregivers), and only involved in topic selection, study design, or results dissemination are not required, but encouraged, to evidence ethics training (see HRPP Policy No. 10.0, Sect. 2.1). If necessary, an IRB Committee chair may solicit an external consultant to determine whether proposed investigators are qualified to participate in the research project (HRPP Policy No. 10.0), as outlined in the application. The IRB will review and vote on PCOR protocols, per HRPP Policy No. 7.0
3.0 SCIENTIFIC REVIEW

The IRB evaluates the scientific or scholarly validity of the research (using its own expertise, the expertise of the GHS Department Review Committee, or the scientific review committee of the entity submitting the study for approval by a GHS IRB) to determine whether the research uses procedures consistent with sound research design, whether the research design is sound enough to reasonably expect the available nonclinical and clinical information on an investigational product to support the proposed clinical trial, and the importance of the knowledge expected to result from the research. The IRB is responsible for ensuring the research’s risk/benefit justifies participation by individuals or communities. All protocols, except retrospective review of medical records or anonymous surveys, must undergo a clinical scientific review (affirming the proposed study’s clinical relevance and potential to inform/improve clinical practice). The clinical scientific review occurs within the protocol’s host department. Investigators provide a GHS IRB Scientific Review Form signed by the host department’s departmental research group (or designated authority) prior to IRB submission. If the host department’s research review group does not include individuals positioned to evaluate the proposal’s clinical scientific merit, the OHRP Medical Director will recruit an expert unaffiliated with the protocol to provide the review.

4.0 MATERIALS REVIEWED BY THE IRB

- For initial review of research by a convened IRB, all IRB members (including alternate members) will review the following materials in enough depth to discuss the information when they are present at the convened meeting:
  - The IRB application;
  - Proposed consent document;
  - Recruitment materials;
  - Any other materials containing relevant information to determine whether the proposed research fulfilled the criteria for approval that includes sufficient information for the IRB to determine whether the research meets the regulatory criteria.
- For initial review of research by a convened IRB, at least one IRB member will review in depth:
  - The full protocol;
  - Any relevant grant applications;
  - Evidence of research qualifications of investigator, which may include curriculum vitae or other relevant documentation.
  - Study Brochure (when one exists)
  - Any other relevant materials;

5.0 REVIEW CRITERIA

In light of the information provided in the research plan of the protocols, the IRB is to determine, in accordance with the following criteria, that human research subjects’ protection is adequate: 21 CFR 56.111 and 45 CFR 46.111
1. Risks to subjects are minimized.
2. Risks, if any, to a subject are reasonable in relation to anticipated benefits and the importance of knowledge that may reasonably be expected to result.
3. Selection of subjects is equitable. In making this assessment, the IRB shall take into account the purposes of the research, the setting in which the research will be conducted, and the population from which subjects will be recruited.
4. Legally effective consent form is obtained (please refer to Policies and Procedures entitled “Informed Consent”).

5. Consent will be appropriately documented (please refer to Policies and Procedures entitled “Informed Consent”).

6. The research plan makes adequate provision for monitoring the data collected to ensure the safety of the subject.

7. There are adequate provisions to protect the privacy of the subject and to maintain the confidentiality of data.

8. Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as persons with acute or severe physical or mental illness, or persons who are economically disadvantaged, appropriate additional safeguards have been included in the study to protect the rights and welfare of the subjects.

6.0 REVIEW DECISIONS

APPROVED: Acceptable as is. No changes are required. Criteria for IRB approval have been met (i.e. 45 CFR 46.111 and 21 CFR 56.111).

ACCEPTED PENDING MODIFICATIONS: Minor, specific changes are required. Criteria for IRB approval have been met (i.e. 45 CFR 46.111 and 21 CFR 56.111) except specific, non-substantial revisions are required. Member comments must be directive requesting simple concurrences or specific, non-substantive changes. Upon receipt of the required changes, the Committee Chair or another member designated by the Chair will verify that the appropriate additions/corrections were made and will either approve the study or return it to full committee.

DEFERRED FOR RE-REVIEW: Substantial modifications and/or additional information (e.g. details, clarifications, justifications) are required that are directly relevant to the Criteria for IRB approval (i.e. 45 CFR 46.111 and 21 CFR 56.111). Deferring a protocol requires that the study with the additional information or modifications be reviewed by Full Board at a convened meeting.

DISAPPROVED: Criteria for IRB are not met (i.e. 45 CFR 46.111 and 21 CFR 56.111). Only the full Board may disapprove a study. Disapprovals should be rare and may occur in one or two ways:

- After multiple attempts (i.e. typically at least two deferrals) have been made to resolve the issues, the Full Board and the Investigator reach an impasse. At the discretions of the IRB, the investigator may be invited to a meeting, or the IRB may assign a committee to meet with the investigator. The IRB may also honor a request from the investigator to present his or her case to the board or a subcommittee.
- The study is disapproved outright because the Full Board determines that the science is clearly inadequate, the resources to conduct the study are not available, or that the research is inappropriate. In the first case, the IRB may ask the investigator to seek scientific review and redesign the project and submit an application.

TABLED: Criteria for a convened Full Board meeting are not met (e.g. loss of quorum; non-scientific member not present) and/or appropriate expertise is not available at the meeting. Study will be reviewed at the next meeting of the duly constituted Full Board.

The IRB Chairperson or the Chairperson’s designee may subsequently approve on behalf of the IRB under an expedited process a research protocol or informed consent form that has been revised in
response to a contingent approval (i.e. where revisions require only simple concurrence by the investigator and the investigator concurs).

With a contingent approval, the PI must respond in writing specifically to each IRB comment point by point. If the revisions requested by the IRB are not received within 60 days after the date of the IRB notification, the study will be closed.

In extenuating circumstances, the PI may submit a written appeal to the IRB Chairperson for an extension to the 60-day submission deadline for revisions to conditional approvals.

**Review More Often Than Annually**

Based on risks being considerable, direct benefits to subjects questionable, and the studies being potentially non-therapeutic, the IRB will determine whether a project requires more than annual review and may require an appropriate monitoring procedure that could include monitoring of the consent process, observation of the research procedures, formulation of a data and safety monitoring plan, and review of research related records.

7.0 **IRB RECORDS**

The IRB shall prepare and maintain adequate documentation of IRB activities, including the following: [21 CFR 56.115](https://www.gpo.gov/fdsys/search/fdsys.search?sid=39050c44a4ddc8f807e60f4b7d99e1e5) and [45 CFR 46.115](https://www.gpo.gov/fdsys/search/fdsys.search?sid=39050c44a4ddc8f807e60f4b7d99e1e5)

1. Copies of all research proposals, reviews, scientific evaluations, if any, that accompany the proposals, DHHS approved sample consent document and protocol, when they existed, approved consent documents, progress reports submitted by investigators, and reports of injuries to subjects.
2. Minutes of IRB meetings.
3. Records of continuing review activities including the timeliness of progress reports, and the IRB decision to append, terminate or allow continuing as approved of previously approved activities.
4. Copies of all correspondence between the IRB and the investigators.
5. A list of IRB members identified by name, earned degrees, representative capacity, indication of experience such as board certifications, licensures, etc., sufficient to describe each member’s chief anticipated contributions to IRB’s deliberations, and any employment or other relationship between each member and the institution (i.e. full-time employee, part-time employee, a member of governing panel or board, paid or unpaid consultants).
6. Written procedures for the IRB regarding initial and continuing review; prompt reporting of changes in approved research; prompt reporting of unanticipated problems involving risks to human subjects; reporting of any serious or continuing non-compliance with federal regulations or GHS policies and procedures; and suspension or termination of IRB approval.
7. Statement that significant new findings developed during the course of the research, which may regulate to the subject’s willingness to continue participation will be provided to the subject and copies of the statements of significant new findings provided to participants.
8. Notification to the full committee by inclusion on the IRB agenda of items given approval with expedited review.
9. Notification to the full committee by inclusion on the IRB agenda of items given permission to start accrual after satisfactory completion of committee required modifications.
10. The records shall be retained for at least 3 years and records relating to research which is conducted shall be retained for 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of federal agencies or departments at reasonable times and in a reasonable manner.
- If a protocol is cancelled without participant enrollment, IRB records will be maintained for at least 3 years after cancellation.

11. For initial and continuing review of research by the expedited procedure:
   - The specific permissible category(ies);
   - Description of action taken by the reviewer;
   - Any findings required under the regulations.

12. Unless documented in the IRB minutes determinations required by the regulations and protocol specific findings supporting those determinations for:
   - Waiver of alteration of the consent process;
   - Research involving pregnant women, fetuses, and neonates;
   - Research involving prisoners;
   - Research involving children.

13. For each protocol’s initial and continuing review, the frequency for the next continuing review.

14. In order to allow a reconstruction of a complete history of IRB actions related to the review and approval of the protocol, the IRB records include copies of:
   - Investigator brochure, if any.
   - Scientific evaluations, when provided by an entity other than the IRB.
   - Recruitment materials.
   - Consent documents.
   - Data and safety monitoring reports, if any.
   - Modifications to previously approved research.
   - Significant new findings.
   - Unanticipated problems involving risks to participants or others.
   - Documentation of non-compliance.

15. IRB records document the justification for exempt determination.

16. IRB records document determinations required by lases, regulation, codes, and guidance.

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

To promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct, and reporting of research is free from bias resulting from researcher financial conflicts of interest. This policy applies to externally funded research, regardless of the funding sources, as well as to research that does not have external funding.

2.0 CONFLICTS OF INTEREST FOR STUDIES FUNDED BY THE US PUBLIC HEALTH SERVICE (PHS)

2.1 Definitions

a. Investigator
A principal investigator, project director, co-investigator, research staff and any other person, regardless of title or position, who is responsible for the design, conduct or reporting of sponsored research (project) results, including collaborators and consultants.

b. GHS Conflict of Interest Committee (GHS COIC)
The Committee comprised of the OHRP Medical Director and the Director of Corporate Integrity that will review disclosures and relevant features of the sponsored project(s). Per the review, the Committee will recommend Investigators make any modifications necessary to manage, reduce or eliminate financial conflicts of interests related to the project.

The OHRP Medical Director is responsible for timely relaying the COIC recommendations to the study’s IRB Chair of record. The Chair or proxy (e.g., IRB Coordinator) will subsequently inform the committee as necessary.

The convened IRB will review the proposed management plan. The IRB has final authority to approve the management plan. The IRB Chair of record will notify the Medical Director and COIC subsequent to management plan approval.

OHRP COIC will maintain records related to COI disclosures, and their accompanying management plans, for at least three years from research completion.

Examples of management plans include:

- Prohibiting the conduct of the research at GHS if the conflict cannot be managed.
- Requiring another researcher conduct the research, or conduct parts of the research such as recruitment and obtaining consent.
• Require monitoring of the research, or parts of the research such as the consent process.
• Management may include a retrospective review and a mitigation report if necessary.
• Other management activities as determined by the GHS COIC.

c. Financial Interest
An interest in a Business consisting of: (1) any stock, stock option or similar ownership interest in such Business, but excluding any interest arising solely by reason of investment in such Business by a mutual, pension, or other institutional investment fund over which the Faculty Member does not exercise control; or (2) receipt of, or the right or expectation to receive, any income from such Business (or from an agent or other representative of such Business), whether in the form of a fee (e.g., consulting), salary, allowance, forbearance, forgiveness, interest in real or personal property, dividend, royalty derived from the licensing of Technology, technology transfer, patents, gifts, rent, capital gain, real or personal property, or any other form of compensation, or any combination thereof whose value exceeds $5,000.

d. Significant Financial Interest
A Financial Interest held by an Investigator, or the Investigator's spouse or dependent children that reasonably appear to be related to the Investigator's Institutional Responsibilities and that consists of one or more of the following:

1. Remuneration including, but not limited to salary, consulting fees, honoraria, and paid authorship received from a publicly traded company during the twelve-month period preceding the date on which an Investigator is making a disclosure, and/or an equity interest (e.g. stock, stock options, or other ownership interest) held in such publicly traded company, if the aggregate value of such remuneration, plus the value of the equity interest as of the date of disclosure, exceeds $5,000 for studies; or
2. Remuneration (including, but not limited to, salary, consulting fees, honoraria and paid authorship) received from a non-publicly traded company during the twelve-month period preceding the date on which an Investigator is making a disclosure, if the remuneration exceeds the amount stated above, or there is specific permission granted to use another triggering amount from the OHRP Medical Director; or
3. Any equity interest in a non-publicly traded company or business, regardless of value; or
4. Intellectual property rights and interests (e.g. patents and copyrights), upon receipt of income related to such rights and interests.
5. Any reimbursed travel or travel expenses paid on an Investigator’s behalf related to his/her institutional responsibilities, including circumstances when the exact monetary value of the travel is not readily available. This requirement does not apply to travel that is reimbursed by a Federal, state or local government, an institution of higher education, an academic medical center or research institute that is affiliated with an institution of higher education.

**Significant Financial Interest does not include:**

1. An Employee's salary or royalties received from the Greenville Health System; or
2. Income from seminars, lectures or teaching engagements sponsored by a federal, state or local government agency or an institution of higher education; or
3. Income from service on panels for a federal, state or local government agency or institution of higher education.
e. Institutional Responsibilities
The institution has the responsibility to educate investigators and research staff about disclosures and responsibilities related to financial conflict of interest.

- Education is required of each individual initially and at least every four years.
- Education is required immediately when:
  - Financial conflict of interest policies are revised in a manner that changes investigator requirements.
  - An investigator is new to the organization.
  - An investigator is non-compliant with financial conflict of interest policies and procedures.

f. Related to the research
Financial interest related to the research means a financial interest in the sponsor, product or service being tested. A researcher’s financial interest is considered related to the research when the researcher and/or research staff is engaged in the research (i.e., interacting or intervening with participants, obtaining consent, conducting analysis of data). Example of persons not engaged include providing advice about the design of studies, conducting analysis of de-identified information, or providing information about research (where a clinician does not recruit or obtain consent). When a person has a financial interest, but is not engaged in PHS-funded research, that interest is not considered related to PHS-funded research for purposes of compliance with PHS funded research conflict of interest requirements.

2.2 CONFLICTS OF INTEREST WHICH MUST BE DISCLOSED BY INVESTIGATORS

A Significant Financial Interest is that held by the Investigator in which the value of the interest could directly or significantly affect the design, conduct or reporting of the research; a proprietary interest in the tested product, including, but not limited to, a patent, trademark, copyright or licensing agreement; any equity interest in the sponsor of a covered study, i.e., any ownership interest, stock options, or other financial interest who value cannot be readily determined through reference to public prices; any arrangement where the value of the ownership interests would be affected by the outcome of the research or ownership interests that exceeds $5,000 in any one single entity when aggregated for the immediate family. This requirement applies to all covered studies, whether ongoing or completed; any equity interest in a publicly held entity or non-publicly held entity that exceeds $5,000 in value. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for 1 year following completion of the study; and significant payments of other sorts, which are payments that have a cumulative monetary value of $5,000 or more made by the sponsor of a covered study to the investigator or the investigator’s institution to support activities of the investigator exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following completion of the study.

The GHS Financial Conflict of Interest form must be updated on an annual basis by either completing the Investigator and IRB Member Conflict of Interest form located on the GHS website [http://www.ghs.org/eirb](http://www.ghs.org/eirb) or during Continuing Review via the eIRB Continuing Review module.
The process to obtain financial disclosures from investigators and research staff requires that any change in financial information regarding a study sponsored by the US Public Health Service must be immediately reported to the Office of Corporate Integrity within 30 days of acquisition or discovery.

CONFLICT OF INTEREST EDUCATION

OHRP Leadership will periodically re-educate investigators and research staff about Conflict of Interest issues and self-assessment. Education may occur individually (e.g., consultation prior to or during eIRB application submission) or in group didactic sessions (e.g., Research Division Advisory Council; GHS Research Education Series, corporate communication).

3.0 CONFLICTS OF INTEREST FOR STUDIES NOT FUNDED BY THE US PUBLIC HEALTH SERVICE (PHS)

3.1 Definitions

a. Investigator
A principal investigator, project director, co-investigator and any other person, regardless of title or position, who is responsible for the design, conduct or reporting of sponsored research (project) results, including collaborators and consultants.

b. GHS Conflict of Interest Committee (GHS COIC)
The Committee comprised of the Chairman of the three IRBs that will review disclosures and relevant features of the sponsored project(s) and, on the basis of the review, to recommend to the Investigator any modifications necessary to manage, reduce or eliminate any financial conflicts of interests related to the project.

c. Financial Interest
An interest in a Business consisting of: (1) any stock, stock option or similar ownership interest in such Business, but excluding any interest arising solely by reason of investment in such Business by a mutual, pension, or other institutional investment fund over which the Faculty Member does not exercise control; or (2) receipt of, or the right or expectation to receive, any income from such Business (or from an agent or other representative of such Business), whether in the form of a fee (e.g., consulting), salary, allowance, forbearance, forgiveness, interest in real or personal property, dividend, royalty derived from the licensing of Technology, technology transfer, patents, gifts, rent, capital gain, real or personal property, or any other form of compensation, or any combination thereof whose value exceeds $5,000.

d. Significant Financial Interest
A Financial Interest held by an Investigator, or the Investigator's spouse or dependent children that reasonably appear to be related to the Investigator's Institutional Responsibilities and that consists of one or more of the following:

1. Remuneration including, but not limited to salary, consulting fees, honoraria, and paid authorship received from a publicly traded company during the twelve-month period preceding the date on which an Investigator is making a disclosure, and/or an equity interest (e.g. stock, stock options, or other ownership interest) held in such publicly traded company, if the aggregate value of such remuneration, plus the value of the equity interest as of the date of disclosure, exceeds $5,000 for studies; or

2. Remuneration (including, but not limited to, salary, consulting fees, honoraria and paid authorship) received from a non-publicly traded company during the twelve-
month period preceding the date on which an Investigator is making a disclosure, if
the remuneration exceeds the amount stated above, or there is specific permission
granted to use another triggering amount from the OHRP Medical Director; or
3. Any equity interest in a non-publicly traded company or business, regardless of
value; or
4. Intellectual property rights and interests (e.g. patents and copyrights), upon
receipt of income related to such rights and interests.
5. Any reimbursed travel or travel expenses paid on an Investigator’s behalf related
to his/her institutional responsibilities, including circumstances when the exact
monetary value of the travel is not readily available. This requirement does not
apply to travel that is reimbursed by a Federal, state or local government, an
institution of higher education, an academic medical center or research institute that
is affiliated with an institution of higher education.

**Significant Financial Interest does not include:**
1. An Employee's salary or royalties received from the Greenville Health System;
or
2. Income from seminars, lectures or teaching engagements sponsored by a federal,
state or local government agency or an institution of higher education; or
3. Income from service on panels for a federal, state or local government agency or
institution of higher education.

**e. Institutional Responsibilities**
The institution has the responsibility to educate investigators and research staff about
disclosures and responsibilities related to financial conflict of interest.
- Education is required of each individual initially and at least every four years.
- Education is required immediately when:
  o Financial conflict of interest policies are revised in a manner that
    changes investigator requirements.
  o An investigator is new to the organization.
  o An investigator is non-compliant with financial conflict of interest
    policies and procedures.

**3.2 CONFLICTS OF INTEREST WHICH MUST BE DISCLOSED BY INVESTIGATORS**

A significant financial interest is an interest held by the investigator in which the value of the
interest could directly or significantly affect the design, conduct or reporting of the research;
a proprietary interest in the tested product, including, but not limited to, a patent, trademark,
copyright or licensing agreement; any equity interest in the sponsor of a covered study, i.e.,
any ownership interest, stock options, or other financial interest who value cannot be readily
determined through reference to public prices; any arrangement where the value of the
ownership interests would be affected by the outcome of the research or ownership interests
that exceeds $5,000 interest in any one single entity when aggregated for the immediate
family. This requirement applies to all covered studies, whether ongoing or completed; any
equity interest in a publicly held entity or non-publicly held entity that exceeds $5,000 in
value. The requirement applies to interests held during the time the clinical investigator is
carrying out the study and for 1 year following completion of the study; and significantly
payments of other sorts, which are payments that have a cumulative monetary value of
$5,000 or more made by the sponsor of a covered study to the investigator or the
investigator’s institution to support activities of the investigator exclusive of the costs of
conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following completion of the study.

The GHS Financial Conflict of Interest form must be updated on an annual basis by either completing the Investigator and IRB Member Conflict of Interest form located on the GHS website [http://www.ghs.org/eirb](http://www.ghs.org/eirb) or during Continuing Review via the eIRB Continuing Review module.

**Corrective Action and Management Plan:**

When individual conflicts of interest are identified, they are managed by the GHS Office of Corporate integrity, which may develop a management plan when appropriate. This plan and procedure includes consultation between the OHRP Medical Director and the GHS Corporate Compliance Officer. In instances where OHRP stakeholders identify a potential conflict, OHRP Stakeholders will notify the Institutional Official/Chief Science Officer. The Institutional Official and Executive Director of the Office of Corporate Integrity will confirm conflict exists and determine whether to disallow individual investigators or suspend the study. Conditions for disallowing or suspending the entire study include, but are not limited to, determining the Conflicted Investigator may exert a disproportionate influence on the investigative team despite exclusion from study team (e.g., directly supervision other team members). The Institutional Official and Executive Director of Corporate Integrity, with guidance from OHRP leadership, will notify the Conflicted Individual of the management conflict plan and provide appropriate updates to GHS governance and leadership. The records related to disclosure and management of financial conflicts of interest will be maintained for at least three years from completion of research.

3.3 **WEB POSTING OF FINANCIAL CONFLICT OF INTEREST INFORMATION**

This policy and subsequent updates are included on the internet.

a) For each financial conflict of interest the committee identifies, the Institution will disclose the following information;

1. The covered individuals name;
2. The covered individuals title and role with respect to the research;
3. The name of the entity in which the significant financial interest is held;
4. The nature of the significant financial interest that constitutes a financial conflict of interest; and
5. The approximate value of the significant financial interest by range or, if the dollar value cannot be determined by reference to public prices or other reasonable measures of fair market value, a statement to that effect.

b) The approximate dollar value of the significant financial interest shall be provided within the following ranges if it can be determined by public access or other reasonable measures of fair market value:

1. $0 - $4,999
2. $5,000 - $9,999
3. $10,000 - $19,999
4. Amounts between $20,000 - $100,000 by increments of $20,000; or
5. Amounts above $100,000 by increments of $50,000.

c) The institution will update the information required by this section annually and
make the information required by this section available not later than the 60th day
after the financial conflict of interest is identified.
d) The information must note that it is current as of the date listed and is subject to
updates.
e) The information required by this section must remain available for five years
after its most recent update.
f) For PHS-funded research, in regard to project directors, principal investigators,
and other senior or key personnel, this information must be available BEFORE
expending PHS funds.

4.0 ORGANIZATIONAL CONFLICT OF INTEREST

An organizational conflict of interest may exist when GHS has a financial interest(s) in research
that potentially conflicts with clinical care. Organizational conflicts of interest may include:
- Licensing, technology transfer, and patents, when GHS owns the intellectual property
- Investments of GHS, in excess of $500,000
- Gifts, when the donor has an interest in the research in excess of $500,000
- Financial interests of senior administrators in excess of $250,000
- Other financial interests that are determined to be a conflict of interest

When organizational conflicts of interest are identified, they are managed by the GHS Office of
Corporate integrity, which may develop a management plan when appropriate. This plan and
procedure includes consultation between the OHRP Medical Director and the GHS Corporate
Compliance Officer. In instances where OHRP stakeholders identify a potential conflict, OHRP
Stakeholders will notify the Institutional Official/Chief Science Officer. The Institutional Official
and Executive Director of the Office of Corporate Integrity will confirm conflict exists and
determine whether to suspend the study. Reporting on review and outcomes will be provided to
the GHS board.

5.0 FINAL DETERMINATION REGARDING CONFLICTS OF INTEREST (REVIEW OF
DISCLOSURES)

Any disclosure of an interest of $5,000 or greater will be reviewed by the GHS Research Conflict of
Interest Committee (OHRP Medical Director and GHS Corporate Compliance Officer).

For any Public Health Services (PHS) funded study (Public Health Service means the Public Health
Service of the US Department of Health and Human Services, and any components of the PHS to
which the authority involved may be delegated, including the National Institutes of Health (NIH))
where financial interest exceeds $5,000 a report must be made to the GHS Research Conflict of
Interest Committee. The GHS Research Conflict of Interest Committee has the responsibility and
authority regarding the acceptability of a management plan for conflicts of interest. The GHS
Research Conflict of Interest Committee will notify the Principal Investigator in writing of its
decision.
6.0 SANCTIONS

Failure to comply with this Policy will be grounds for disciplinary action pursuant to the relevant GHS policies.

In addition, federal regulations may require reports to the federal sponsor of any information which may show a violation of GHS policy. GHS may require mandatory education, monitoring of research, suspension of research privileges, suspend or terminate research or enact other sanctions as appropriate. In addition, sponsors may suspend or terminate the award and/or debar an Investigator from receiving future awards in the event of failure to comply with applicable federal regulations on disclosure, review, and management of significant financial interests related to federally sponsored projects.
1.0 QUALIFICATIONS TO PERFORM HUMAN RESEARCH

The Greenville Health System (GHS) Office of Human Research Protection (OHRP) is responsible for deciding who can perform any research study involving human subjects at GHS. Prior to approving any study, OHRP, or affiliate IRB, is required to assure that the Principal Investigator (PI), any co-investigators, the study sponsor/representative and the research staff possess appropriate qualifications and general resources to conduct the research project and assure protection of subjects’ rights and welfare.

The GHS OHRP requires the PI to have the appropriate background and training to conduct the research required for each study. The GHS OHRP, or affiliate IRBs, will decide on the qualifications for PIs. Principal investigators are required to be members of the GHS medical professional staff, nursing staff, employees of GHS, or a faculty member a GHS-affiliated institution. Professionals in training (i.e. medical students, nursing students, students of affiliate institutions, or resident physicians) are not permitted to be Principal Investigators. Fellows may be principal investigators if they have medical staff privileges at GHS.

Additionally, the GHS IRB may require that a physician with admitting privileges and appropriate expertise be substantially involved with the research project, particularly if the research study or procedures are greater than minimal risk.

2.0 PI RESPONSIBILITIES WHEN CONDUCTING RESEARCH AT GHS

The principal investigator (PI) is responsible for the design and implementation of ethical research, consistent with three ethical principles delineated in the Belmont Report:
- Respect for Persons (individual autonomy; protection of individuals with reduced autonomy)
- Beneficence (Maximize benefits and minimize harms)
- Justice (equitable distribution of research costs and benefits)

Clinical trials should be conducted in accordance with the ethical principles having their origin in the Declaration of Helsinki and that are consistent with good clinical practice and the applicable regulatory requirements.

The principal investigator (PI) is responsible for personally conducting or supervising the conduct of human-subjects research and for protecting the rights, safety, and welfare of the subjects enrolled in the research. The PI must conduct research ethically and comply with all applicable federal, state, and local laws and regulations, institutional policies, and requirements or determinations of the Greenville

The PI is responsible for ensuring the protocol design anticipates potential harm to the study subject and includes procedures mitigating potential harm to study participants.

The Principal Investigator is ultimately responsible for overseeing all research conducted, and all IRB communication (via the Office of Human Research Protection) regarding that research. All official IRB correspondence is directed to the PI. However, the PI may request that another research staff member also receive IRB communication; however, the Principal Investigator retains responsibility for all aspects of the research protocol.

The PI must provide the IRB office with current contact information, including mailing address, telephone number, fax number and email address. The PI must promptly inform the office whenever this information changes.

The IRB may request additional information from the PI or the sponsor to enable appropriate review of research applications.

1. **Supervising the conduct of human-subject research**
   The PI may delegate study-related tasks, but must supervise personnel delegated to those tasks. PIs must ensure study personnel:
   - are sufficiently trained and experience to perform study-related tasks delegated to them;
   - understand the research goals; and
   - abide by the IRB-approved protocol, including subject recruitment and consent procedures described in the protocol summary.

   The PI should consider a supervision and oversight plan for the research. Supervision should be appropriate to the personnel’s expertise, the nature of the research, and the subject population.

2. **Protecting the rights, safety, and welfare of research subjects**
   The PI or other identified qualified individual(s) must be available to provide study subjects reasonable medical care for any medical problems arising during research participation that are, or potentially related to the research. Additionally, when research participation might impact the subject’s health and/or medical care, the PI should inform the subject’s primary care physician about the subject’s participation in the research if the subject has a primary care physician and if the subject agrees to the primary care physician being informed.

   When protecting the rights, safety, and welfare of research subjects, the PI must ensure that:
   - subjects comprehend the consent process, and only enroll subjects’ demonstrating informed understanding of the research study.
   - S/he or other identified, qualified individual(s) provides study subjects with reasonable medical care for any adverse events, including clinically significant laboratory values, related to research;
   - S/he or another specific qualified individual is available to study subjects to answer questions or provide care during the conduct of the research; and
   - S/he and all research staff conducting the study adhere closely to the research plan, and inclusion/exclusion criteria, safety assessments, safety monitoring and reporting of adverse events and procedures to protect privacy of subjects and confidentiality of identifiable data, in order to minimize risks to subjects.
The PI should not commence the research without adequate resources to protect participating subjects, and should cease research if necessary resources become unavailable. These resources may include research personnel, space, equipment, time, and availability of medical or psychological care for problems arising during research participation.

3. **More Specific Responsibilities of Principal Investigators**

The PI must:

- Ensure GHS IRB approval prior to research initiation
- Compliance with all applicable GHS IRB policies, procedures, decisions, conditions and requirements.
- Conduct research in accordance with the GHS IRB approved protocol, including, when applicable, the approved recruitment and consent procedures;
- Provides evidence of research qualifications through up-to-date curriculum vitae, résumé, or other relevant documentation requested by the sponsor, the IRB, or the regulatory authority.
- Follow the clinical trials randomization procedures, if any, and ensure deviations only in accordance with the protocol or subject protection. If the clinical trial is blinded, the investigator promptly documents and explains any premature unblinding to the sponsor.
- Be familiar with the appropriate use of the investigational product, per the protocol, in the current investigator brochure, in the product information, and other sponsor-developed information sources.
- Ensure a qualified physician (or dentist, when appropriate), is responsible for all clinical trial-related medical (or dental) decisions.
- Obtain informed consent (when required) in accordance with federal regulations, approved by the IRB and documented using the current GHS IRB approved research consent form;
- When drugs, biological products, and devices are being investigated or used, they are managed and controlled as required by institutional policy, and when applicable, FDA regulations 21 CFR 312 and 21 CFR 812;
- Changes to the GHS IRB approved protocol and/or the research consent form are not initiated without prospective GHS IRB approval unless necessary to eliminate apparent immediate hazards to the subject;
- Unanticipated problems involving risks to subjects or others (including adverse events) are reported promptly to the GHS IRB in accordance with GHS IRB policy;
- The researcher reports adverse events or laboratory abnormalities identified in the protocol as critical to safety evaluations to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
- The PI reports all serious adverse events (SAEs) to the sponsor except for those SAEs that the protocol or other document (e.g., investigator’s brochure) identifies as not needing immediate reporting. The PI follows regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authority and the IRB.
- For reported deaths, the researcher supplies the sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).
- The PI provides written reports to the sponsor, the IRB, and, where applicable, the organization on any changes significantly affecting the conduct of the clinical trial or increasing the risk to subjects.
- When applicable, Data and Safety Monitoring Board/Data Monitoring Committee or other monitoring group reports are submitted promptly to the GHS IRB for review;
- Continuing review is conducted prior to expiration of GHS IRB approval in accordance with GHS IRB policy and the federal regulations;
- Should GHS IRB approval lapse, research procedures, such as recruitment and enrollment of subjects, study procedures on currently enrolled subjects, review of health/medical records, collection of tissue or other samples, or analysis of data, are not conducted until the GHS IRB re-approves the research or until special permission is obtained from the GHS IRB to continue previously enrolled subjects because it is in their best interests to do so;
- When the research has been completed or is being closed out prior to completion, a final continuing review report is submitted to the GHS IRB;
- The PI ensures the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.
- Although a subject is not obliged to give his or her reasons for withdrawing prematurely from a clinical trial, the investigator makes a reasonable effort to ascertain the reason, while fully respecting the subject’s rights.
- If the PI terminates or suspends a clinical trial without prior agreement of the sponsor, the PI informs the organization, sponsor, and the IRB.
- If the IRB terminates or suspends approval of the clinical trial, the PI promptly notifies the sponsor.
- Upon completion of the clinical trial, the investigator informs the organization; the IRB with a summary of the trial’s outcome; and the regulatory authority with any reports required.
- Adequate and accurate research reports are kept and retained as required by the GHS IRB and, when applicable, by the sponsor, OHRP, or FDA.
- Research records are made available to the GHS IRB, the sponsor, and when applicable, the Office for Human Research Protections (OHRP), and the Food and Drug Administration (FDA) upon request for monitoring and oversight of the research.
- To comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic a Form 1572 must be completed and submitted to the IRB. Additionally, any change or amendment to Form 1572 (e.g. new investigator added to the study) made after the initial upload in the eIRB must be submitted to the IRB.

2.1 TRAINING OF INVESTIGATORS

All researchers (principal investigators, co-investigators, other research staff, and students) involved in human subject research must complete training prior to study protocol approval and research initiation. Researchers are required to pass the CITI Training Course (or other appropriate training approved by the OHRP Medical Director) per institutional instructions and appropriate training modules located on the CITI web page.

Continuing Research Education: All researchers (principal investigators, co-investigators, and research staff) actively involved in human subject research must complete continuing education training every three (3) years, via the CITI Training Course.

If the sponsor provides training materials for investigators in the conduct of the study, the PI must ensure the staff receives and reviews these materials and/or participates as necessary in any in-person training sessions pertinent to their role in the study.

The PI must have a detailed plan for the supervision and oversight of a study. Supervision and oversight should be provided even for individuals who are highly qualified and
experienced. A plan might include the following elements, to the extent they apply to a particular study:

- Routine meetings with co-investigators and study staff to review progress of the study and update them on any changes to the study or other procedures;
- Routine meetings with the sponsor’s monitors;
- A procedure for correcting problems identified by co-investigators or study staff, outside monitors or auditors, or other parties involved in the conduct of a study;
- A procedure for documenting the performance of delegated tasks in a satisfactory manner and, when appropriate, verifying findings (e.g. observation of the performance of selected assessments or independent verification by repeating selected assessments);
- A procedure for ensuring the consent process is being conducted in accordance with federal regulations 45 CFR 46 and 21 CFR 50 and GHS IRB requirements and that study subjects understand the nature of their participation, risks, etc.;
- A procedure for ensuring that information in source documents is accurately captured on the Data Collection Forms, Case Report Forms, or elsewhere as appropriate to the study;
- A procedure for dealing with data queries and discrepancies identified by the study monitor or other individuals responsible for oversight of the study; and/or
- Procedures for ensuring co-investigators and study staff comply with the IRB approved protocol and reporting requirements of the IRB and sponsor.

3.0 TRANSFERRING A PROTOCOL TO ANOTHER INVESTIGATOR

If a PI leaves an institution where GHS is the IRB of record, all of his/her approved research studies must be transferred or closed.

When an investigator chooses to transfer his status as PI on an approved protocol to another investigator, the IRB must be notified. The new investigator must be eligible and qualified to serve as a Principal Investigator (PI). To affect this transfer, the PI of record must submit an Amendment form to the IRB stating that the protocol should be transferred to another investigator who will assume responsibility for the research. This letter is co-signed by the existing PI and the new PI. The PI must also submit to the IRB appropriate changes to consent forms, recruitment materials, etc. as part of the protocol transfer. The Office of the IRB will notify the existing PI and the new PI in writing when the amendment is approved.

4.0 COMMUNICATION REGARDING THE HUMAN RESEARCH PROTECTION PROGRAM (HRPP)

Any personnel engaged in research at GHS may voice any questions or concerns, related to the Human Research Protection Program (HRPP) (e.g. IRB procedures and policies), to the Institutional Official, or the IO’s designee. If the concern involves the Institutional Official, the GHS General Counsel may receive and respond to the concern. Persons may also report concerns anonymously to the GHS General Counsel. The Institutional Official and the GHS General Counsel will respond within ten business (10) days, and address patient safety or regulatory compliance issues immediately.
1.0 SCOPE

The Greenville Health System (GHS) Institutional Review Board (IRB) utilizes an electronic submission process (eIRB) for all protocol submissions. All study-related documents requiring GHS IRB review must be attached electronically to the protocol application. Documents must be submitted in either Microsoft Word or Adobe PDF format.

security and data management standards to maintain the security of all medical and financial information are applied to the eIRB system. The standard for maintaining the physical security and integrity of the data and system, backup and recovery, and user access security are GHS standards applied to all enterprise wide systems.

The application will be housed at the South Carolina Research Authority (SCRA).

2.0 ACCESS CONTROLS

- eIRB represents a closed system, meaning an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system.

- Access is limited to authorized individuals. Authorized individuals must have both a User ID and password, and have been assigned a role within the eIRB system.

- Access to the eIRB system requires an authorized account (User ID and password), which is unique to one individual. An individual without an authorized account, or whose account has been disabled, cannot access the eIRB system. Individuals work only under their own authorized account. The establishment, control and security of GHS accounts are directed by GHS Office of Human Research Protection
  - Key Points for the GHS Policy
    - The account (user name and password) is unique to one individual such that no two individuals have the same combination of user name for an active account.
    - Individuals are held accountable and responsible for action initiated under their account.
    - The identity of the individual is verified before an account is established.
    - Controls are followed for loss management procedures to disable compromised accounts.

- The eIRB system uses defined levels of access called user roles to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output, alter a record or perform the operation at hand. Individuals using the eIRB system are assigned a specific combination of user roles which define the information an
individual can access and his/her ability to create or modify information. User roles are assigned based on the specific function or role an individual plays in the development, conduct or oversight of research projects.

- Study staff roles (PI/Co-I, Study Coordinator and Study Staff Members), IRB Committee Chair roles and IRB Committee Member roles may be assigned by the IRB Administrative Staff or the GHS Office of Human Research Protection Medical Director.
- IRB Administrative roles, Department/Section approver role, ancillary committee approver roles and all other administrative roles may be assigned by the IRB Administrative Staff or the GHS Office of Human Research Medical Director.
- The role of System Administrator requires the approval of HSSC.

3.0 ELECTRONIC SIGNATURE

- Electronic signature means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual’s handwritten signature.

- Each electronic signature in eIRB is unique to one individual and is not reused by or reassigned to anyone else.

- Electronic signatures in eIRB employ two distinct identification components, a user name and password.

- Medical Policy and Procedure establishes controls to ensure user name and password security and integrity.

- Executed electronic signatures are linked to their respective electronic records to ensure that the signature cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

- The signed electronic record contains information associated with the signing that clearly indicates the printed name of the signer; date and time when the signature was executed and the meaning.

- All actions executed by a signing authority are logged.

4.0 AUDIT TRAIL

- The eIRB system uses a secure, computer-generated date and time-stamped audit trail to automatically record the date and time of operator entries and actions that create, modify, or delete electronic records. Previously recorded information is not obscured by record changes. Audit trail information is retained at least as long as that required for the subject electronic record and is available for review and copying.

  - Key points for Academic Computing Policy
    - Access is limited to authorized individual
    - Changes are documented
    - Detected Discrepancies are reported
5.0 VALIDATION

- Click Commerce releases periodic service packs and upgrades in order to improve performance and functionality as well as to stay compliant with new Microsoft technologies as they are released. Click Commerce uses feedback from the Click Compliance Consortium, a consortium of Click Commerce Research Extranet customers, to guide ongoing product development and to beta test new releases of service packs and upgrades.

- Design level validation is maintained by Click Commerce.

6.0 SYSTEM CONTROLS

- All changes to the eIRB computerized system, such as software upgrades, security and performance patches, and equipment or component replacement are evaluated and tested to ensure the integrity of the data is maintained.

- All changes to the system are documented.

- All versions of the software are documented.

7.0 CONTINGENCY PLAN

- In the event that the eIRB system is not functional for an extended period of time due to server malfunction, a backup “warm” site will be enabled on a separate server in order to maintain the integrity and continuity of data within the site.

- In the event the eIRB system is not functional and the outage is anticipated to be 24 hours or less, only protocol activity that is immediately required to address issues related to the safety, rights or welfare of research subjects will be acted upon. The determination as to whether an issue needs to be immediately addressed will be made by either the GHS OHRP Medical Director or an IRB Chair. Documentation will be made on paper forms made available to the study team by either web posting, faxing, or in the IRB Office. Following resumption of the system the study team will transfer all paper information to the eIRB system and attached scanned copies of all paper documents.

- In the event the eIRB system is not functional and the outage is anticipated to last greater than 24 hours, the IRB will shift to a paper based system. Documentation will be made on paper forms made available to the study team by either web posting, faxing, or in the IRB Office. Following resumption of the system the study team will transfer all paper information to the eIRB system and attached scanned copies of all paper documents.

- In the event the eIRB system is not functional and the system cannot be restored, active protocols will be identified by querying the user base, querying other GHS databases, and contacting sponsoring agencies. Copies of required documents will be requested in order to reconstruct files. The IRB will review each reconstructed study file.

The user base will be notified to suspend all study activities except where necessary to ensure the safety, rights or welfare of enrolled subjects until the IRB has reviewed the reconstructed study file. Such a failure to suspend will be reported to OHRP, FDA and all other applicable agencies as required by regulation.
8.0 BACK-UP AND RECOVERY

A complete backup is scheduled every Friday and incremental backups are scheduled all other days. SCRA retains backups for 6 weeks. This backup routine is standard for production, staging, and development servers.
1.0 PREPARING A PROTOCOL FOR SUBMISSION TO THE IRB

All protocols must be submitted to the GHS IRB using the eIRB web-based system, which can be accessed at http://eirb.healthsciencesc.org

Following the guidelines on the GHS Office of Human Research Protection website http://university.ghs.org/research-protection/ investigators must submit (as appropriate for the study) a copy of the study protocol, consent form(s), recruitment materials and advertisements, investigational test article brochure and grant application to the Office of Human Research Protection IRB. IRB staff review the submission for completeness, ask the PI to submit any missing elements, and then make a preliminary determination whether the subsequent review should be full-board or expedited. For full-board reviews, submissions are assigned to the next available IRB agenda, as appropriate for the committee expertise, and sent to each committee member prior to the assigned meeting.

The following items must be included with the GHS IRB submission:

- Title of study;
- Purpose of study;
- Funding sponsor of the study;
- A Written Study Protocol: The IRB submission must contain a complete study protocol, as indicated in the eIRB application found at http://eirb.healthsciencesc.org. The protocol will particularly outline the study design. This includes describing proposed:
  - study participants (and affirming access to the target population)
  - instruments
  - procedure (including a recruitment plan ensuring participant accrual necessary to detect intervention impact)

If a protocol is submitted for review and the committee members believe that there is insufficient information to enable an appropriate review, a request for additional information may be made to the PI. Requests may include, but are not limited to the following:

- Results of previous research;
- Subject inclusion/exclusion criteria;
- Justification for use of any special/vulnerable subject populations and/or justification for exclusion of any particular group;
- Study design, including justification for the proposed sample size;
- Description of procedures to be performed for monitoring data to ensure the safety of participants or a reason why this is not appropriate;
- The methods of identifying and contacting potential subjects;
- The processes for obtaining informed consent, including setting, subject autonomy concerns, language interpretation issues, vulnerable populations issues;
- The procedures for documentation of informed consent, including any procedures for obtaining assent form minors, using witnesses, waiver of consent, translation of forms, and informed consent form storage;
- Compensation to subjects for their participation and justification;
- Compensation for research-related injury;
- Provisions for protection of subject’s privacy and confidentiality of data;
- Extra costs to subjects for their participation in the study;
- Extra costs to third party payers because of subject’s participation.
- Assessment of time the research team will need to conduct and complete the research (projected project duration).
- Number of qualified staff necessary to complete the proposed work.
- Assessment of facilities necessary to conduct the proposed work.
- Availability of medical or psycho-social resources participants may need as the result of the research.

2.0 RELEVANT MATERIALS: THE FOLLOWING ITEMS MUST BE PROVIDED WHEN APPLICABLE:

- Investigator’s Brochure and/or Device Manual (when one exists). A copy of the investigator brochure will be provided to the primary and secondary reviewers.
- Questionnaires, interview scripts, subject diaries, etc. Any documents that will be used by subjects, or by research staff to obtain information from subjects, will be submitted with the application. These will be provided to the primary and secondary reviewers. Any committee member may review these documents via the eIRB application.
- The Proposed Informed Consent Document. See Policy No. 13.0 for information related to Informed Consents.
- Research Advertising and Recruitment Materials. Any advertising or publicity information including recruitment letters, flyers, posters, public service announcements, newspaper, radio and television advertisements, and Internet content seeking study subjects for research that falls under the scope of authority of the GHS IRB must be approved by the GHS Institutional Review Board.

These materials may be submitted by the PI to the IRB either with the initial application or subsequent to approval as an amendment. None of these materials may be used until IRB approval is obtained.

3.0 SIGNATURES REQUIRED

3.1 Principal Investigators (PI) must submit all new studies; continuing reviews; amendments/revisions and reportable events using the eIRB modules. The PI submit button on these modules replaces the PI’s signature on the paper forms.

4.0 IMPACTED ANCILLARY SERVICE UNITS

Certain types of protocols (e.g. those involving use of radiation; surgery; pharmacy; laboratory, nursing; biomedical engineering and infectious disease) are required to be reviewed by one or more
GHS departments/committees prior to IRB review. These departments/committees will access the new study application via the eIRB review system at [http://eirb.healthsciencesc.org](http://eirb.healthsciencesc.org) where they may approve, require modification or disapprove the protocol. Once their review has been completed, the new study application will be forwarded, electronically, to the appropriate IRB coordinator for review and/or scheduling for either expedited or full board review.

- Nursing Research Council Approval is required when any part of the research protocol involves any, or all, of the following:
  - The study involves nursing practice
  - PI is a registered nurse
  - PI is working on a nursing academic degree
  - The nursing staff is the primary focus of the study

- Pharmacy Approval is required when any part of the research protocol requires the participation of GHS Pharmacy services. The Department of Pharmacy Services of GHS is responsible for overseeing the storage, distribution and control of all medications administered to patients throughout the system including investigational medications. The Joint Commission, DHEC, and the South Carolina Board of Pharmacy mandate this responsibility. Office-based outpatient studies may be exempt.

- Surgery Approval is required when any part of the research protocol requires the participation of GHS Surgery services.

- Laboratory Approval is required when any part of the research protocol requires the participation of GHS Laboratory services.

- Radiology Approval is required when any part of the research protocol requires the participation of GHS Radiology services.

- Human Resource Approval is required when the study requires a survey (electronic, paper, personal or telephonic) of some or all of GHS employees. A copy of the proposed survey, including methodology and timeframe must be attached to the application prior to department approval. The GHS Director of Employee Services will review on behalf of Human Resources.

One member of the IRB will be identified to function as the “primary reviewer”. Another member of the IRB will be identified to function as the “secondary reviewer”. Full review capabilities of all related materials will be available via the eIRB system at [http://eirb.healthsciencesc.org](http://eirb.healthsciencesc.org). All members of the IRB will have access and be able to review and/or comment through either public and/or private comments via the eIRB system.

The PI, Co-investigator, or the GHS Study Sponsor/Representative, must be present at an IRB meeting to present the project to the IRB membership. After sufficient discussion, the members will vote on the application to approve/disapprove, or defer a decision until additional information is provided, or further expert review is obtained. The decisions will be based on the votes of the majority of the voting members present.

During the voting process, the PI, Co-investigator and/or the GHS Study Sponsor/Representative will be excused from the room. If the PI, Co-investigator or the GHS Study Sponsor/Representative is a member of the IRB, it will be documented in the minutes that he/she was excused for the vote.

The PI will receive written communication outlining the decisions of the IRB.

5.0 **CLINICAL TRIALS REGISTRATION POLICY AND PROCEDURES**

The Food and Drug Administration (FDA) and the International Committee of Medical Journal Editors (ICMJE) each have their own registration requirements. While some of the requirements
overlap, there are also significant differences. In order to comply with new laws and preserve the ability to publish in ICMJE journals both sets of requirements must be met.

**FDA CLINICAL TRIALS REGISTRATION**

In September 2007, the FDA Amendment Act expanded the ClinicalTrials.gov requirements previously established in the 1997 Modernization Act (FDAMA) requiring registration of trials testing drugs for life threatening diseases and conditions. This new FDA policy:

1. Expands the types of trials that must be registered to all clinical trials for drugs, devices, and biologics with the exception of Phase I drug trials and small device feasibility studies.
2. Increases the data elements that must be included in the registration.
3. Results of trials must be registered within 3 years of the completion of the primary aim of the study. The process for registration of results is in development.

**ICMJE CLINICAL TRIALS REGISTRATION**

Effective July 1, 2008, the ICMJE revised its policy of June, 2005. The new policy requires the registration of all clinical trials including Phase I and pharmaco-kinetic trials. ICMJE defines clinical trials as:

1. Any human research project that prospectively assigns human subjects to an intervention or comparison group to study the relationship between a medical intervention and a health outcome.
1.0 FEDERAL REGULATIONS REGARDING INFORMED CONSENT

Federal regulations require that no investigator may involve a human being as a subject in a research project without obtaining legally effective informed consent of the person or the person’s legally authorized representative (LAR). The investigator must provide the prospective subject or the LAR sufficient opportunity to consider whether or not to participate and must minimize the possibility of coercion or undue influence. The information that is given to the subject or LAR shall be in language understandable to the subject or LAR.

21 CFR 50.25(a) and 45 CFR 46.116 require that the elements of informed consent criteria be met. The information that should be provided to each subject has been incorporated in the GHS Informed Consent Template, which is available from the IRB office. The template is provided to the investigator. Informed consent forms must be submitted in the prescribed template format for review by the IRB. The IRB may waive the requirement for the use of the IRB format as appropriate.

The investigator is responsible for obtaining a signed consent form from the patient, or their Legally Authorized Representative, and this responsibility cannot be delegated to pharmacy, nursing, or other hospital personnel. For all studies involving greater than minimal risk, as defined in 45 CFR 46.102(i), and all studies involving investigational drugs or investigational devices, a licensed physician investigator must obtain informed consent. Study nurses or others may assist the physician investigator, but physician investigator should be actively involved and not delegate this vital investigator responsibility. In non-interventional studies, or minimal risk studies it may be appropriate for nurses or other study staff to obtain consent, with “back up” provided by physician investigators. If the investigator is proposing that a non-physician staff obtain consent, the investigator must provide rationale, qualifications, and training of the relevant study staff at the time of original submission and this must be approved by the IRB prior to initiation of the study. Everyone who obtains consent must be a Principal Investigator or Co-investigator.

If the patient is a minor or is unable to provide consent, it is the investigator’s responsibility to obtain consent from the patient’s legal guardian/representative.

2.0 ELEMENTS OF INFORMED CONSENT

The following are required elements in an informed consent form (ICF):
- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject’s participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others that may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the subject, and their important potential benefits and risks.
- A disclosure that the monitor, the auditor, the IRB, and the regulatory authority will be granted directed access to the participant’s original medical records for verification of clinical trial procedures or data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the participant or the participant’s legally authorized representative is authorizing such access.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the IRB, the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, the sponsor (or others, as appropriate) may inspect the records.
- A disclosure that is from the approval of the IRB.
- A statement that the description and results of the research will be posted on clinicaltrials.gov. The statement should inform the participant or the participant’s legally authorized representative that a description of the clinical trial will be available on this website as required by U.S. Law. The website will not any information that can identify the participant. At most, the website will have a summary of the results. The participant or participant’s legally authorized representative should be informed they are free to search this website at any time.
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects’ rights, and whom to contact in the event of a research-related injury to the subject.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- When appropriate, anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent.
- When appropriate, 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.
- When appropriate, the consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- When appropriate, a statement that significant new findings, developed during the course of the research, which may relate to the subject’s willingness to continue participation will be provided to the subject.
- When appropriate, the approximate number of subjects involved in the study.
- When appropriate, any additional costs to the participant that might result from participation in the research.
- When appropriate, the amount and schedule of payments.
3.0 HOW MUST CONSENT BE OBTAINED?

- For any study involving more than minimal risk, as defined by 45 CFR 46.102(i), informed consent must be obtained, in person from the participant, or their Legally Authorized Representative, by the Principal Investigator, or Co-investigator.
- The investigator must be sure that all consent forms are signed, dated and witnessed and placed in the participant’s study record prior to study participation. The original should be retained in the participant’s study record at the clinical research site. Case histories (patient charts) will also document that Informed Consent was obtained prior to the subject’s participation in the study.
- Prior to participation in the trial, the participant or the participant’s legally authorized representative should receive a copy of the signed and dated written consent document and any other written information provided to the participants along with a copy of the signed and dated written consent document placed in the medical record.
- A verbal approval does not satisfy the 21 CFR 56.109(c) requirement for a signed consent document, as outlined in 21 CFR 50.27(a). However, for studies meeting the criteria for minimal risk, as defined by 45 CFR 46.102(i), informed consent can be obtained by mail, telephone, fax, or in person. Informed consent documentation requirements 21 CFR 50.27 permit the use of either a written consent document that embodies the elements of informed consent or a “short form” 21 CFR 50.27(b)(2) written consent document stating that the elements of informed consent required by 21 CFR 50.25. This needs to be mailed, or faxed to the subject, or the subject’s legally authorized representative, prior to it being presented orally. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the signed and dated short form or written consent document.
- If a participant is unable to read or if a legally authorized representative is unable to read, an impartial witness should be present during the entire informed consent discussion.
  - After the written consent document and any other written information to be provided to participants, is read and explained to the participant or the participant’s legally authorized representative, and after the participant or the participant’s legally acceptable representative has orally consented to the participant’s participation in the trial and, if capable of doing so, has signed and personally dated the consent document, the witness should sign and personally date the consent document.
  - By signing the consent document, the witness attests that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the participant or the participant’s legally authorized representative, and that consent was freely given by the participant or the participant’s legally authorized representative.
  - Prior to participation in the trial, the participant or the participant’s legally authorized representative should receive a copy of the signed and dated written consent document and any other written information provided to the participants along with a copy of the signed and dated written consent document placed in the medical record.

4.0 REVIEW OF INFORMED CONSENT

The IRB reviewers and the IRB coordinators review the informed consent form using the Informed Consent checklist of required and optional elements 45 CFR 46.116 and 21 CFR 50.25. Changes are
marked on the informed consent form and returned to the PI for revision. Once the informed consent form is modified and approved, the PI is sent a validated copy, stamped with the date of the IRB approval (“approved”) and the date through which the form is valid (“consent expires”). All signed informed consent forms must be retained after the end of the study for a period of three years by the PI.

The IRB may observe or arrange for observation of the consent process or research to ensure that the consent process is properly conducted to protect participants and/or may require verification that no material changes have been made in the study from a source other than the investigator.

5.0 INFORMED CONSENT CATEGORIES

Written Consent
Informed consent must be documented on a stamped GHS IRB approved consent form unless these requirements are specifically waived or modified by the IRB. The consent form (ICF) must be signed and dated by the subject or his/her legally authorized representative. The expiration date on the ICF is the last day of the current IRB approval. The date of the subject’s signature on the ICF must be prior to the expiration date stamped on the ICF.

Waiver of Documentation of Informed Consent
Federal regulations permit an IRB to waive the requirement for the investigator to obtain a signed consent form for some or all subjects if the IRB finds and documents in the minutes either:

- That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject’s wishes will govern; or
- That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

When granting waivers of the requirement to obtain written consent documentation of the consent process, the IRB considers requiring the investigator to provide subjects with a written statement regarding the research.
Waiver of Informed Consent

Federal regulations permit an IRB to approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent. Permission is conditioned upon the IRB finding and documenting that:

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

The IRB may allow waiver of consent on a case-by-case basis. The IRB is allowed to waive parental permission by determining that the criteria for waivers and alterations are met. The IRB review (whether expedited or full board) must ensure that each protocol satisfies each of the above criteria, the regulatory criteria is met, and that the research is not regulated by the FDA. If the research is FDA regulated, the IRB is prohibited from waiving or altering the consent process. In instances where consent is waived, it remains essential that the protocol describes the appropriate procedures for maintenance of confidentiality in the protocol. The IRB is allowed to waive the requirement to document the consent process by determining that the regulatory criteria for waivers are met. When the IRB considers waiving the requirement to obtain written documentation of the consent process, the IRB reviews a written description of the information that will be provided to participants or the participant’s legally authorized representative.

The waiver of consent process and waiver of parental permission for the Public Demonstration Project follows DHHS regulations. The research is conducted by or subject to the approval of state or local government officials and is not FDA regulated. The research or demonstration protocol is designed to study, evaluate, or otherwise examine:

- Public benefit or service programs.
- Procedures for obtaining benefits or services under those programs.
- Possible changes in or alternatives to those programs or procedures.
- Possible changes in methods or levels of payment for benefits or services under those programs.

The research cannot practicably be carried out without the waiver of consent. This waiver or alteration of consent process follows the guidelines of research that is not FDA-regulated. The waiver of consent process varies with the waiver of parental permission when permission is not a reasonable requirement. This is when the research, that is not FDA regulated, is designed for conditions or for a participant population for which parental or guardian permission is not a reasonable requirement to protect the participants. In this case, an appropriate mechanism for protecting the children who will participate as participants in the research is substituted.

6.0 INFORMED CONSENT FOR NON-ENGLISH SPEAKING PARTICIPANTS

Special consent-related issues may arise when research participants do not speak or read English. Federal regulations 45 CFR 46.116 and 46.117 and 21 CFR 50.20, require that informed consent be solicited in a language participants (or authorized representative) understand and, in most situations, that the informed consent be documented in writing.

Where informed consent is documented in accordance with 45 CFR 46.117(b)(1), the written consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. Subjects who do not speak English should be presented with a
consent document understandable to them. Federal regulations strongly encourage the use of this procedure whenever possible.

Alternatively, 45 CFR 46.117(b)(2) and 21 CFR 50.25 permits oral presentation of informed consent information in conjunction with a short form written consent document (stating that the elements of the consent have been presented orally) and a written summary of what is presented orally. Oral presentation requires a witness, and the subject must be given copies of the short form document and the summary. As required by 21 CFR 50.27, a copy of the consent form must be given to each participant. For non-English speaking participants, this document is the translated consent form.

When this procedure is used with subjects who do not speak English, (i) the oral presentation and the short form written document should be in a language the subject understands; (ii) the IRB-approved English language informed consent document may serve as the summary; and (iii) the witness should be fluent in both English and the language of the subject.

At consent, (i) the short form document should be signed by the subject (or the subject’s legally authorized representative); (ii) the summary (i.e. the English language informed consent document should be signed by the person obtaining the consent as authorized under the protocol; and (iii) the short form document and the summary should be signed by the witness. Then the person obtaining consent is assisted by a translator, the translator may serve as the witness.

The IRB must receive all foreign language versions of the short form document as a condition of approval under the provisions of 45 CFF 46.117(b)(2). Expedited review of these versions is acceptable if the protocol, the full English language informed consent document, and the English version of the short form document have already been approved by the convened IRB.

GHS Language Services must either translate or approve a translated consent for content. A completed IRB Language Services Form (see Appendix B) must be submitted with the translated consent.

A completely translated copy of the informed consent and a complete back-translation done by a qualified translator(s) must be submitted to the IRB before the ICF is approved. Expedited review of these versions is done if the protocol and the full English version of the ICF have already been approved.

While a translator may facilitate conversation with the participant, Investigators may not substitute routine ad hoc oral translation of the consent document for a written translation.

The IRB is responsible for determining which of the procedures at 45 CFR 46.117(b) is appropriate for documenting informed consent in protocols that it reviews.
CONTINUING REVIEW PROCESS

1. The IRB must continually review ongoing research projects. Requirements for Continuing Review (CR) are provided to the PI with the IRB approval letter. Some research projects (e.g. those with higher risks) may require that reviews occur more frequently than annually. Additionally, the IRB may require review after a predetermined number of subjects have been enrolled into the protocol. The frequency of review will be clearly defined in the IRB approval letter.

2. It is the responsibility of the PI to ensure that the research protocol does not expire. If an application for continuing review is not received by the IRB office, the study will be terminated.

3. Continuing Review must be substantive and meaningful. The IRB applies the same criteria for approval of continuing review applications as it does for initial applications. For this reason the IRB must receive enough information to ensure continued protection of human subjects.

4. To apply for continuing review and approval, the principal investigator shall complete the eIRB Continuing Review Module application. The information to be provided by the investigator shall include the following:
   - Current risk-benefit analysis;
   - Description of subject experiences;
   - Amendments to the protocol not previously submitted;
   - Number of subjects enrolled in the study, number of subjects completed, number of subjects; withdrawn, and number of subjects still being treated;
   - Reason for subject withdrawals;
   - Any preliminary results from the study;
   - Adverse reactions not previously reported;
   - Anticipated enrollment in the study;
   - The expected duration of the study;
   - Any additional information concerning the state of knowledge about the study question (particularly other information that might change the assessment of clinical equipoise or the risk: benefit assessment);
   - Any presentations or publications of study findings.
   - Data Safety Monitoring Board report (if applicable).

5. For continuing review of research by a convened IRB, all IRB members (including alternate members) will review the following materials in enough depth to discuss the information when they are present at the convened meeting:
- The IRB application;
- The full protocol;
- Other materials containing relevant information to determine whether the proposed research fulfilled the criteria for approval (e.g. reviewer checklist for continuing review);
- The current consent document;
- Any newly proposed consent document;
- A status report on the progress of the research.

For continuing review of research by a convened IRB, at least one IRB member reviewed in depth the complete protocol including any protocol modifications previously approved by the IRB.

6. Based on the information in the Continuing Review application the staff in the IRB office determines whether the CR can receive expedited review or whether it must be reviewed by a convened IRB. Continuing reviews may be expedited when the research was:
   - Approved by expedited review on initial approval and no changes in risks have occurred
   - Approved by convened IRB but the research is now closed to accrual of new participants, all participants have completed all research-related interventions, and the research remains active only for long-term follow-up on participants.
   - Approved by convened IRB but no participants have been enrolled and no additional risks have been identified.
   - Approved by convened IRB but now the remaining research activities are limited to data analysis.
   - Not conducted under an investigational new drug application or investigational device exemption, and the categories for expedited review for new protocols do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

7. Continuing review must continue until:
   - The research is permanently closed to the enrollment of new participants; and
   - All participants have completed all research-related interventions; and
   - Collection and analysis of private identifiable information has completed.

8. If a PI has failed to provide CR information to the IRB or the IRB has not reviewed and approved a research study by the approval expiration date specified by the IRB, the research must stop, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection of private identifiable information. Interventions and interactions on current participants continued only when the IRB found an over-riding safety concern or ethical issue involved such that it is in the best interests of individual participants to continue treatment. Enrollment of new subjects cannot occur.

9. When continuing review of a research protocol does not occur prior to the end of the approval period specified by the IRB, the research project lapses. Data may not be collected and patients cannot be enrolled; however, any required treatment of participants may continue. At the discretion of the Chair, Vice-Chair and/or Medical Director, the IRB may complete continuing review for the project as soon as possible but no later than the next scheduled IRB meeting, at which time a new expiration date will be established.

Investigators may resume the human subjects research activity once continuing review and approval by the IRB full board and/or expedited procedure has occurred. The IRB shall document why the lapse in IRB approval occurred, and the steps that the IRB and the Principal Investigator are taking to prevent any such lapse of approval of the project from
occurring in the future. Such expiration of IRB approval does not need to be reported to OHRP as a suspension of the IRB approval under HHS regulations. The Principal Investigator should pay close attention to the expiration date of the IRB approval that occurs after a lapse in the research project. No approval period granted by the IRB at any time may exceed 365 days but in some instances, such as Phase I projects, may be shorter.

10. The IRB may terminate or suspend a previously approved study prior to its expiration date if evidence is discovered through monitoring or other review procedures that warrants such action.

2.0 NOTIFICATION OF INVESTIGATORS

The IRB promptly reports all findings and actions in writing to the PI and, if required, to a sponsor or regulatory agency. These include written communications from the IRB to the PI for additional information, for conveying IRB findings and for acknowledgement of notifications received. IRB records and communications are maintained in permanent study files located in the IRB office. After the study is closed, files are maintained for a minimum of three years, or longer if required for a particular study.
PI must promptly request, from the IRB, approval for proposed changes in research activity by completion of the Amendment module via the eIRB, at website http://eirb.healthsciencesc.org. Information must include complete detailed documentation (redlined version of the informed consent and/or protocol, advertisements, etc.) as to what changes or modifications are being proposed and the justification (rationale), as well as an assessment of the impact of the changes on the risks to participants. Your amendment will not be reviewed without a summary of changes and a redlined version of the changes. PI’s must also report to the IRB the premature completion of a research study.

No amendments or changes may be implemented without approval of the IRB, except to eliminate apparent immediate hazards to research subjects. In such instances the IRB will review the change to determine whether the change is consistent with ensuring the participants’ continued welfare. Implementation of changes without IRB review and approval that were not done to eliminate apparent immediate hazards to research subjects will be considered research misconduct (please refer to HRPP Policy No. 22.0 entitled “Ethical Standards and Misconduct in Research”). The date of approval of an amendment does not change the date by which the regularly scheduled continuing review of the project is to be completed.

All amendments, advertisements or other changes (including minor consent form changes) are reviewed, findings are documented in IRB minutes, and written notification of the IRB decision is provided to the PI. The IRB uses the criteria to approve modifications to previously approved research when the modifications affect one or more criteria. The actions taken to ensure that proposed changes in approved research during the period for which IRB approval had already been given cannot be initiated without IRB approval. Changes in approved research that are initiated without IRB approval to eliminate apparent immediate hazards to the participant are (a) promptly (no longer than within 30 days) reported to the IRB, (b) reviewed by the IRB to determine whether each change was consistent with ensuring the participants’ continue welfare.

If the IRB approves research with conditions:
- Minor or prescriptive changes or requirements may be reviewed for approval by the IRB chair or designated IRB member.
- 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.
- The date of approval is the date the conditions were determined to be met.
- If the research expires before the conditions are reviewed and approved, all research activities must stop until approval is obtained.
Two members of the IRB will be assigned as primary reviewers for the revisions and will review all materials submitted. They will present the revisions to the committee at the IRB meeting. All IRB members (including alternate members) will review all modified documents in enough depth to discuss the information when they are present at the convened meeting. The committee will vote on the application to approve, disapprove, or defer a decision until additional information is provided. The decisions will be based on the votes of the majority of the voting members present.

Audits may be conducted by the IRB if there is reason to suspect a change in protocol has occurred without IRB approval. The GHS Office of Human Research Protection is responsible for these audits.
1.0 SCOPE

Research activities involving no more than minimal risk to human participants and involving only procedures listed in one or more of the following categories may be reviewed by the IRB through the expedited review procedure, 45 CFR 46.110 and 21 CFR 56.110.

A. Clinical studies of drugs and medical devices only when condition (1) or (2) is met.

1. Research on drugs for which an investigational new drug application 21 CFR Part 312 is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review).
2. Research on medical devices for which:
   a. an investigational device exemption application 21 CFR Part 812 is not required; or
   b. the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

B. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

1. from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amount drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
2. from other adults and children considering the age, weight, and health of the participants, the collection procedures, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

C. Prospective collection of biological specimens for research purposes by noninvasive means. For example:

- Hair and nail clippings in a non-disfiguring manner;
- Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
- Permanent teeth if routine patient care indicates a need for extraction;
- Excreta and external secretions (including sweat);
- Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;
- Placenta removed at delivery;
• Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
• Supra and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
• Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
• Sputum collected after saline mist nebulization.

D. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples:

1. physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject’s privacy;
2. weighing or testing sensory activity;
3. magnetic resonance imaging;
4. electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electoretinography, ultrasound diagnostic infrared imaging, Doppler blood flow, and echocardiography;
5. moderate exercise, muscular strength testing, body composition assessment and flexibility testing where appropriate given the age, weight, and health of the individual.

E. Research involving materials (data documents, records or specimens) that have been collected or will be collected solely for non-research purposes (such as medical treatment or diagnosis).

F. Collection of data from voice, digital, or image recording made for research purposes

G. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural benefits or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

H. Continuing review of research previously approved by the convened IRB as follows:

1. Where
   a. the research is permanently closed to the enrollment of new participants;
   b. all subjects have completed all research-related interventions;
   c. the research remains active only for long-term follow-up of participants; or
2. No subjects have been enrolled and no additional risks have been identified;
3. The remaining research activities are limited to data analysis.
I. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories (B) through (H) do not apply but the IRB has determined and documented at a convened meeting that research involves no greater than minimal risk and no additional risks have been identified.

Minimal Risk: A risk is minimal if 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. 45 CFR 102(i) and 21 CFR 50.3(k).

Research in any of these categories may require review at a convened meeting of the GHS IRB if the circumstances of the proposed research involve more than minimal risk.

2.0 PROCEDURES

A. An IRB may use the expedited review procedure to review proposals that fall within the requirements as set forth in 45 CFR 46.110. Specifically:

1. research involving only procedures which are included on the list of procedures eligible for expedited review and which are determined by the reviewer to involve no more than minimal risk, or

2. minor changes in previously approved research during the period (of one year or less) for which approval was authorized.

3. The IRB should not base their determination solely on risks (e.g. greater than minimal risk) because a Principal Investigator can make major modifications that are not greater than minimal risk, but which may still warrant substantial review.

B. Expedited review shall be conducted by the IRB Chairperson, the IRB Vice-Chairperson, or an experienced member of the IRB designated by the Chair or Vice-Chairperson. An experienced IRB member is a member with sufficient time served with the IRB and experienced in reviewing submitted research. A Chair determines that a member qualifies as an experienced member by evaluating one or more of the following: a) their qualifications as a researcher, if applicable; b) IRB service; and c) member knowledge of the regulations and guidance concerning human subjects in research. The IRB member conducting the expedited review may exercise all the authorities of the IRB except that the reviewer may not disapprove the research. The reviewer reviews evidence of scholarly capability of investigator which may be demonstrated by any of the following documents: curriculum vitae, résumé, documentation of research collaboration or other materials.

C. The reviewer may also refer other research protocols to the full committee whenever the reviewer believes that full committee review is warranted.

D. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that the risk related to invasion of privacy and breach of confidentiality is no greater than minimal.
E. In addition, the expedited review procedures may not be used for classified research involving human subjects. Classified research is research that has a security classification established by an authorized agency of the federal government. GHS does not conduct classified research.

F. When the expedited review procedure is used, the committee will be notified of any such approval by inclusion on the IRB agenda.

3.0 MINOR CHANGES IN APPROVED RESEARCH

The reviewing IRB Chairperson, the IRB Vice-Chairperson, or an experienced member of the IRB designated by the Chair or Vice-Chairperson is responsible for reviewing and determining whether the proposed change (or amendment) is minor, and if minor, may review and approve the change using the expedited review procedure described above.

3.1 The proposed change is considered minor when the research meets all of the following criteria:
- the proposed change does not significantly alter the risk to benefit assessment the GHS IRB relied upon to approve the protocol;
- the proposed change does not significantly affect the safety of subjects;
- the proposed change does not involve the addition of invasive procedures (procedures not otherwise eligible for expedited review, e.g. collection of blood samples in limited amounts);
- the proposed change does not involve the addition of procedures, interactions or interventions that add significant medical, social or psychological risks;
- the proposed change does not involve addition of a vulnerable population in research not otherwise eligible for expedited review; and
- the proposed change does not significantly alter the scientific question or the scientific quality of the study.
The purpose of this policy is to define the applicability of the exemptions from the requirements of 45 CFR 46 and/or 21 CFR 56 and the procedures the Greenville Health System (GHS) Human Subjects Protection Program will follow when conducting review of exempt human-subjects research and clinical investigations.

POLICY STATEMENT:
The GHS Institutional Review Board (IRB) chairpersons, or their designees, are responsible for determining whether a research study is exempt from 45 CFR 46 and 21 CFR 56. Investigators or others within the organization may not make exemption determinations. The GHS chairpersons, and/or their designee, are subject to the GHS Human Research Protection Policy (HRPP Number 6.0) on IRB Member Conflicts of Interest when reviewing and making exemption determinations.

PROCEDURES:
In order to fulfill requirements for the proper review of research, the GHS HRPP evaluates and certifies “exempt” status on appropriate applications. The IRB chair, or proxy (e.g. Vice Chair) assigns applications to this category. The PI must submit the appropriate application, via eIRB, to facilitate IRB review. “Exempt” status does not mean an application is free from IRB oversight. “Exempt” studies are governed by all ethical principles pertaining to human subjects research. “Exempt” status means the IRB judges the study to possess very little associated risks, and only when the sole involvement of human subjects will be in one or more of the categories listed in 45 CFR 46 (b) (1-6) or 21 CFR 56.104.

Exempt research fulfills the Greenville Health System’s ethical standards, such as:
- The research holds out no more than minimal risk to participants.
- Selection of the participants is equitable.
- If there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of the data.
- If there are interactions with participants, the IRB should determine whether there should be a consent process that will disclose such information as:
  - That the activity involves research.
  - A description of the procedures.
  - That participation is voluntary.
  - Name and contact information for the researcher.
- There are adequate provisions to maintain the privacy interests of participants.

The IRB chair is empowered to delegate IRB member designees to help determine whether an application warrants an “exempt” status. Delegation may occur if the chair is not readily available, or if the chair deems a conflict of interest exists, or appears to exist. In this case, the Chair will designate a member...
qualified to determine whether the study qualifies as an exempt study. If the activity does not qualify for exemption, the IRB will notify the investigator via the eIRB module.

The IRB will not create new categories of exempt research.

1. The chair/designee will not consider any research exempt that involves prisoners, sensitive aspects of subject’s behavior, sensitive surveys, or that takes place in settings where subjects have a reasonable expectation of privacy.

2. The chair/designee will not consider any research exempt that involves survey or interview procedures or observation of public behavior of children except for research involving observation of public behavior when the investigator(s) does not participate in the activities being observed.

3. The chair/designee will not consider any research exempt that involves a test article regulated by the FDA unless the research meets the criteria for exemption described in 45 CFR 46.101(b)(6).

4. The IRB chair or designee will review the proposed research and will validate or decline the investigator’s request for exemption, ensure that risks to individuals are minimized, and confirm that the research meets ethical standards. The IRB will document the review and action of the IRB Chair or designee including the category specified in 45 CFR 46.101(b)(16) or 21 CFR 56.104(ad) justifying the classification of exempt.

5. The IRB will promptly notify the PI in writing (via eIRB) of its decision regarding the research. If it is determined that the research is not exempt or if modifications are required such as submission of a consent document or strengthening of protections in place to minimize risks to participants, the IRB will include in its written notification a statement of the reason for its decision and give the PI an opportunity to respond in person or in writing. Final approval of exempt research is pending resolution of all minor modifications identified by the IRB reviewer.

6. If the IRB chair or designee determines that an application does not qualify for exemption, the application will be processed either through Expedited Review or by full IRB review.

7. At the time of approval of exempt protocols, PIs are reminded of the responsibility to report all modifications and unanticipated problems involving risks to subjects or others in accordance with IRB Standard Operating Procedures. The exemption granted is only for the submission as written at the time of the initial review when the decision to exempt was determined. Changes should be reported utilizing the Amendment module via the eIRB. If the submission remains exempt, the investigator will be notified of the decision. If the change(s) require(s) that the research be reviewed using expedited or full board review, the investigator will be notified and asked to submit the appropriate additional documentation for this review.

8. Applications for exempt research are reviewed in the same manner as expedited protocols.
9. Closeout: The principal investigator is responsible for submitting a continuing review application within 30 days of completion or termination of all research activity for a study to provide a final report and request that the IRB close its research records.

EXEMPTION OF RESEARCH INVOLVING CHILDREN
Research that involves children and falls into categories 1-6 described below may be found to be exempt by the IRB. However, the exemption category 2 at 45 CFR 46.101(b)(2) above, pertaining to survey or interview procedures or observations of public behavior, does not apply to research involving children, except for research involving public behavior when the Investigator does not participate in the activities being observed.

EXEMPTION OF RESEARCH INVOLVING PRISONERS
Research under categories 1-6 is not exempt if it involves prisoners. These applications must be submitted for IRB Committee review. Research involving prisoners can be approved under expedited review procedures. However, because of the vulnerability of prisoners, OHRP recommends that all research involving prisoners be reviewed by the convened IRB. If the research is reviewed under the expedited review procedure, OHRP recommends that the IRB member(s) reviewing the research include a prisoner or prisoner representative.

EXEMPT CRITERIA
Unless otherwise required by the IRB, research activities designated in 45 CFR 46 or 21 CFR 56.104(ad), in which the only involvement of human subjects will be in one or more of the following categories, are exempt from this policy:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, where this category of research is not FDA-regulated, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods. Educational¹ research proposals are exempt providing ALL of the following are met:

   a. All of the research is conducted in a commonly accepted educational setting (e.g., a private or public school).

   b. The research involves normal educational practices (e.g., comparison of instructional techniques).

   c. The study procedures do not entail a significant deviation in time or effort from those educational practices already existent in the study site.

   d. The study procedures do not involve an increase in the level of risk or discomfort beyond normal, routine educational practices, including physical education.

   e. The study procedures do not involve deception or withholding of information.

   f. The study procedures do not involve sensitive topics, such as sexual behavior of individual subjects. A sensitive survey is one which deals with socially questionable or highly personal issues or alcohol and/or drug abuse.

   g. Provisions are made to ensure the existence of a non-coercive environment for all students, including those who choose not to participate.
h. The school or other agency grants written approval for the research to be conducted.

i. Educational tests of (i) knowledge, (ii) mastery, or (iii) skills.

¹The No Child Left Behind Act of 2001 (Public Law 107-110) identified 8 categories of protected information for survey responses: political affiliations of student or student's parent; mental or psychological problems of student or student's family; sex behavior or attitudes; illegal, antisocial, self-incriminating or demeaning behavior; critical appraisals of others with whom students have close family relationships; legally recognized privileged or analogous relationships; religious practices, affiliations or beliefs of student or student's parent; and income. Research involving any of the eight identified categories requires written parental informed consent prior to participation of a child.

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability, or be damaging to the subjects' financial standing, employability, or reputation.

Observational Research
Observational research involving sensitive aspects of subjects’ behavior, or in settings where subjects have a reasonable expectation of privacy, is not exempt. Similarly, sensitive survey research is seldom exempt from IRB review (see below for exceptions). A sensitive survey includes questions about illegal activities, or highly personal aspects of the subject’s behavior, life experiences, or attitudes. Examples include chemical or substance abuse, sexual activity or attitudes, sexual abuse, criminal behavior, sensitive demographic data, detailed health history, etc. The potential for provoking a negative emotional reaction from subjects is a principal determining factor in sensitive survey research. In addition, observation of children is not exempt from IRB review if the researcher participates in or influences the observed activities.

Breach of Confidentiality
Additional consideration for exemption includes whether there is a risk associated with a possible breach of confidentiality (i.e., accidental disclosure of drug use to law enforcement personnel). In surveys with potential psychological risk, review of exemption includes risks associated with surveys about sensitive topics as well as those resulting from a breach of confidentiality. When confidentiality is an issue, the presence or absence of subject identifiers may be a decisive factor.

Questionnaires/Surveys/Interviews
Questionnaires or surveys covering sensitive topics may qualify for a request for Exemption, if they fulfill the following:

a. anonymity of the subject is guaranteed,
b. potential subjects are fully informed of the sensitive nature of the topics prior to their participation,
c. the study does not exceed minimal risk; and
d. children are not involved as subjects.

3. Research that is not FDA-regulated and not exempt under category 2 involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (2) (b) of this section, if: (a) the human
subjects are elected or appointed public officials or candidates for public office or (b) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information be maintained throughout the research and thereafter. Copies of the informed consent form and questionnaire or survey instrument(s) to be used must be forwarded to the IRB for review.

4. Research, not FDA-regulated, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Anonymous Data
Investigators should note that a survey is anonymous (if containing PHI, meets the HIPAA de-identified definition) when there is no possible way to identify the participants from the data collected. Data are not anonymous if anyone or any procedure such as accessing a computer database, will identify the subject. In most instances, the omission of names or other specific identifiers, such as social security numbers, is insufficient to qualify a study as anonymous. Sometimes an investigator may preserve a subject’s anonymity while still retaining data on individual characteristics such as age, gender, ethnic origin, occupation, or diagnosis. Anonymity is possible only when studying large samples or populations. When the number of potential participants is small or the research setting is identified, anonymity can be threatened or compromised even when the names are removed from the data.

Existing Data, Documents, and Human Biological Specimens for Nongenetic Research
The source of the data, documents, pathological specimens or diagnostic specimens must be provided to the IRB, along with the name of the gatekeeper of the data, documents, or specimens. The term “existing” refers to the time period that the data and/or material was obtained and does not necessarily mean that the data and/or material was obtained for clinical or diagnostic purposes. OHRP indicates that the term “existing” refers to data, documents, biological material and/or tissue “archived” or “on the shelf” prior to the conceptualization of the research project and prior to review by the IRB.

Research involving existing data, documents and/or specimens is typically exempt under Exempt Category 4 as long the following conditions pertain:

a. The data, documents and/or specimens exist prior to the conceptualization of the research project. This is what was earlier referred to as “archived” or “on the shelf” data and/or documents.

b. The data, documents and/or specimens are publicly available. Data, documents and/or specimens whose access is restricted to select groups are not publicly available.

c. The information from the data, documents and/or specimens must be recorded in such a manner that subjects cannot be identified directly, or through identifiers linked to the subjects.

d. The researcher must provide written confirmation to the IRB that permission for the use of data, documents and/or specimens has been granted by the gatekeeper and that the information is publicly available.

Many agencies and/or departments routinely collect data or information as part of an on-going quality control or quality assurance process. In most situations, the collection of such information does not constitute research and is, therefore, not reviewable by the IRB. In addition, educational agencies may collect information related to student progress or to assess the effectiveness of new programs or projects. As with quality control or quality assurance information, the data collected by educational agencies is
usually not reviewed by the IRB. The IRB becomes involved when researchers wish to access this information for research purposes.

Archived pathology or diagnostic specimens that are considered residual biological material and are destined to be destroyed can be used in research and are considered exempt from IRB review if there are no patient identifiers HIPAA de-identified) linked to the specimen and if the data is not intended to be used in the diagnosis or treatment of a patient. If either of these conditions apply, consent of the research subject is required and the study is not exempt from IRB review. If the data/specimens are collected after the submission of the IRB application, the data is not preexisting or “archived.” When the data/specimen is not “archived” or if the information is recorded with direct or indirect identifying links to subjects, the protocol requires IRB review and may require written informed consent.

Research which includes review of private records involving access to and recording of identifiable information is not exempt from IRB review or HIPAA standards and may require prior written consent of the subjects. Records considered private based on federal and state statutes, including medical records, insurance records, and educational records, may require written authorization by the individual subject or waiver of authorization by the IRB, written assurance to the gatekeeper of the record and IRB review, in order to be used in research.

**Specimen Protocols Ineligible for Exemption**

The IRB is required to review research requesting the use of residual biological material, i.e., blood, tissue, other bodily fluids, etc., that is no longer needed for clinical/diagnostic purposes (“archived” or “on the shelf”) if the material or tissue is not archived prior to submitting the protocol to the IRB.

Material or tissue that has not been archived prior to the submission of the research protocol to the IRB does not qualify for a request for exemption. The IRB is also required to review research with residual material where the investigator intends to identify the patient/subject donor with the acquired sample, either for future purposes or with the intent that the research results may have implications for diagnostic or clinical decisions.

Requests for additional material, i.e., blood, tissue, bodily fluid, from a patient or subject who is scheduled for a diagnostic or clinical procedure are not exempt from IRB review. This type of study would prospectively, or prior to the procedure, request for research purposes, the obtaining of extra material or tissue. IRB review is required regardless of the amount of extra material requested and regardless of the purpose for which it is procured.

Research involving human ova (fertilized and unfertilized) is not exempt.

Specimens received as extra material or extra specimens requested from a physician conducting a clinical procedure are not pre-existing or “archived” and thus require written informed consent from the subject and review by the IRB. If there is a link to the patient’s identity and a possibility that the patient may be contacted in the future, an informed consent document is required. Furthermore, informed consent is required if there is a link to the patient’s identity and a possibility that the research may result in commercial or economic value.

The federal regulations also require that the IRB distinguish between residual material and/or tissue and extra material and/or tissue gathered from diagnostic or clinical procedures to be used in research.

This section does not apply to human biological specimens collected or used for genetic research. There are additional ethical concerns for genetic research that may apply for other types or research with biological specimens. Please contact the IRB for additional information.
5. Research and demonstration projects, that are not FDA-regulated, which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (a) public benefit or service programs; (b) procedures for obtaining benefits or services under those programs; (c) possible changes in or alternatives to those programs or procedures; or (d) possible changes in methods or levels of payment for benefits or services under those programs.

**NOTE:** OHRP has determined that the following criteria **must be satisfied** to invoke the exemption for research and demonstration projects examining "public benefit or service programs" as specified under Department of Health and Human Services (DHHS) regulations at 45 CFR46

   a. The program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act).

   b. The research or demonstration project must be conducted pursuant to specific federal statutory authority.

   c. There must be no statutory requirement that the project be reviewed by an Institutional Review Board (IRB).

   d. The project must not involve significant physical invasions or intrusions upon the privacy of participants.

Institutions should consult with the DHHS funding agency regarding the above conditions before invoking this exemption. In addition, it is extremely important that staff in all DHHS agencies understand and respect the following principles, which are critical to the successful implementation of human subject protections under DHHS regulations:

   a. Institutions conducting (non-exempt) DHHS supported human subjects research must provide OHRP with an acceptable Assurance of Compliance with the human subjects regulations [45 CFR 46]. Under the terms of such Assurances, it is typically the responsibility of the Institutional Review Board (IRB) or other designated institutional official(s), not the investigator, to determine whether research activities qualify for exemption. Institutions holding OHRP approved Assurances generally require that all research involving human intervention/interaction or identifiable private information [45 CFR 46.102(f)(2)] be subjected to independent verification of exempt status.

   b. Institutions may elect under their Assurance not to claim the exemptions provided in the regulations, choosing instead to require IRB review of all research involving human intervention/interaction or identifiable private information.

   c. While DHHS requires neither an Assurance nor a Certification of IRB Review [45 CFR 46] for exempt research, institutional requirements regarding review of such research are, nevertheless, binding on investigators. It would be inappropriate for staff of any DHHS agency to discourage potential awardees from submitting their activities for institutionally required IRB review.

6. Taste and food quality evaluation and consumer acceptance studies, (a) if wholesome foods without additives are consumed; (b) if a food is consumed that contains a food ingredient or an agricultural chemical or environmental contaminant, the food ingredient or agricultural chemical or environmental contaminant is at or below the level and for a use found to be safe by the Food and Drug Administration.
(FDA) or approved by the Environmental Protection Agency or the Food Safety and Inspection Services of the U.S. Department of Agriculture.

7. The following categories of clinical investigations regulated by the FDA (21 CFR 56) are exempt from the requirements of this part for IRB review:

   a. Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

   b. Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

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

   d. Taste and food quality evaluation and consumer acceptance studies, (a) if wholesome foods without additives are consumed; (b) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe by the Food and Drug Administration (FDA) or approved by the Environmental Protection Agency or the Food Safety and Inspection Services of the U.S. Department of Agriculture.

Department or Agency heads retain final judgment as to whether a particular activity is covered by this policy. The Greenville Health System, an institution with a DHHS approved assurance on file, will abide by provisions of Title 45 CFR Part 46 Subparts AD and Title 21 CFR 56.

The IRB retains the right to require oversight and continuing review when warranted by the nature of the research and/or inclusion of vulnerable subject populations even though it may not be required by federal regulation.

This right may be exercised in situations when the IRB:

1. Has sufficient reason, through anonymous reports, to suspect that the research is not being conducted as described in the submitted protocol and no amendments to the protocol have been received, noting changes in the protocol,

2. Receives a complaint from a subject about the conduct of the research,

3. Receives a complaint from another investigator or associate of the researcher,

4. Believes that the research, while meeting the exempt research criteria, could unfairly embarrass individuals, the Greenville Health System or their research affiliates,

5. Has other reasons yet to be determined.

When providing ethical review of exempt research, the reviewing GHS IRB Chair and/or their designee, is also responsible for determining that the research meets the institution’s ethical principles for human subject protection, specifically the Ethical Principles and Guidelines for the Protection of Human Subject Research and the requirements of the Health Insurance Portability and Accountability Act (HIPAA).
If, in the opinion of the IRB chair or their designee who reviews exempt research, a protocol that meets the exempt criteria may conflict with the GHS ethical standards for research, then that individual can seek counsel from the full IRB, senior GHS HRPP staff, or GHS Legal Counsel. The chair should be prepared to discuss the issues of concern with those with whom he consults. After consultation, a summary of the discussion and the final decision will be reported to the appropriate IRB and recorded in the minutes of that meeting.

Studies that meet exemption criteria do not necessarily mean that the investigator is exempt from the need to obtain informed consent from a subject or HIPAA requirements.

The IRB may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency, but not otherwise covered by this policy, comply with some or all of the requirements of this policy. Projects involving classified research cannot be completed by exempt review.

GHS Chairs, and or their designee(s), may restrict, suspend, terminate, or choose not to authorize an IRB’s use of the exempt review procedure.
1.0 PURPOSE

The purpose of this policy is to define the requirements for reporting unanticipated problems involving risks to subjects or others and adverse events to the Greenville Health System (GHS) Institutional Review Board (IRB).

This policy is established to comply with the Department of Health and Human Services (DHHS) regulations at 45 CFR 46.103(b)(5)(i) and 45 CFR 46.108(a) requiring IRBs to have “written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials and the Department or Agency head of any unanticipated problems involving risks to subjects or others.” The Food and Drug Administration (FDA) regulations include the same requirement 21 CFR 56.108(b)(1).

Additionally, federal regulations 45 CFR 46.113 and 21 CFR 56.113 state, “IRBs shall have the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB’s requirements or has been associated with unexpected serious harm to subjects.” To expedite this important authority, investigators must promptly inform IRBs of unexpected adverse events, related to research participation, and involving new or increased risks to participants or others.

2.0 SCOPE

All investigators affiliated with approved studies are subject to this policy. This reporting policy applies to both internal and external adverse events. Internal adverse events are unanticipated problems or adverse events experienced by subjects enrolled in single center or multi-center studies at sites included in the study’s GHS IRB approval. External unanticipated problems or adverse events are those experienced by subjects enrolled in studies at sites that do not rely on the GHS IRB for review.

3.0 DEFINITIONS

Unanticipated Problems Involving Risks to Subjects or Others Events: Any incident, experience, or outcome that meets ALL of the following criteria:
1. Unexpected (in nature, severity, or frequency) given: (a) the research procedures described in the protocol-related documents (e.g., IRB-approved research protocol and informed consent document), and (b) the characteristics of the study population;

2. Related or possibly related to a subject’s participation in the research (here, *possibly related* means that the event is more likely than not related to participation in the research or, there is a >50% likelihood that the event is related to the research procedures); and

3. Places subjects or others at a different or greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

**Adverse Event:** An undesirable and unintended, although typically not unexpected, result of therapy or other intervention (e.g. headache following spinal tap or intestinal bleeding associated with aspirin therapy). Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporarily associated with the subject’s participation in the research, whether or not considered related to the study intervention.

Adverse events encompass both physical and psychological harms. They occur most commonly in biomedical research. Occasionally, however, adverse events may occur in social and behavioral research.

**Serious Adverse Event:** Any adverse event temporally (here, meaning up to 90 days following active study participation completion) associated with the subject’s participation in research meeting any of the following:

- Results in death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect; or
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject’s health and require medical or surgical intervention to prevent one of the other outcomes listed in this definition. (e.g., allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse), (modified from the definition of associated with use of the drug in FDA regulations at 21 CFR 312.32(a)).

**Related to Research** refers to an incident, experience or outcome likely resulting from participation in the research study, occurring up to 90 days following active study participation completion.

**Possibly Related to Research** means that the event is more likely than not related to participation in the research or, that there is a >50% likelihood that the event is related to the research procedures. These definitions and standards are not restricted to research procedures, and pertain to all protocol elements and instruments.

### 4.0 DECIDING IF AN EVENT MEETS THE CRITERIA FOR UNANTICIPATED PROBLEM
It may be difficult to determine whether a particular incident, experience or outcome is unexpected, and whether the incident is related or possibly related to research participation. An incident, experience, or outcome meeting the three criteria above may warrant substantive protocol revisions, informed consent process/document revisions, or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

1. *Is an event unexpected?*

An event is unexpected if it occurs in one or more subjects or others, and the event’s nature, severity, or frequency is not consistent with either:

- The known or foreseeable risk of adverse events associated with the procedures described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) any other relevant sources of information, such as product labeling and package inserts; or
- The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event, and the subject’s predisposing risk factor profile for the adverse event.

2. *Is an event related or possibly related to a subject’s participation in the research?*

Events that are related or possibly related to participation in the research may be caused by one or more of the following:

- The procedures involved in the research;
- An underlying disease, disorder, or condition of the subject;
- Other circumstances unrelated to either the research, or any underlying disease, disorder, or condition of the subject.

In general, events determined to be at least partially caused by study procedures are considered related to research participation, whereas events determined to be solely caused by the subject’s condition or state of illness or other circumstances clearly outside of the study are considered unrelated to research participation.

3. *Does an event suggest that the research places subjects or others at greater risk of harm than was previously known or recognized?*

The first step in assessing whether an adverse event meets the third criterion for an unanticipated problem is to determine whether the adverse event is *serious*. See the definition of “serious adverse event” above (Section 3.0). Adverse events that are unexpected, related or possibly related to participation in research, and serious are the most important subset of adverse events representing unanticipated problems. The reason is such events always suggest that the research places subjects or others at a greater risk of physical or psychological harm than previously known or recognized. These events warrant consideration of substantive change in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects.

Other adverse events that are unexpected and related or possibly related to participation in the research, but not serious, would also be unanticipated problems if they suggest that the research places subjects or others at a greater risk of physical or psychological harm than was
previously known or recognized. These events should also be reported, for consideration of changes, or corrective actions.

4.1 Examples of adverse events that should be considered as unanticipated problems that must be reported to the IRB:

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).

- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).

- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveal higher rates in the drug treatment arm versus control).

- An AE that is described or addressed in the investigator’s brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator’s brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risks to human subjects.

- A serious AE that is described or addressed in the investigator’s brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison).

- Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator’s brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects.

4.2 Differentiating between an Unanticipated Problem and an Adverse Event

By definition, an “unanticipated problem” is unexpected, whereas an “adverse event” may be anticipated or unanticipated. Additionally, an unanticipated problem may involve the increased risk of harm – whether or not any actual harm occurred. To determine whether an event qualifies as an unanticipated problem, consider the following:

- Not all Adverse Events are Unanticipated Problems. Only a small subset of “adverse events” occurring in FDA-regulated clinical trials and other types of studies constitute unanticipated problems and therefore must be reported promptly to the IRB. Many events that are required to be reported to the sponsor or federal agency are not unanticipated problems.

- An unanticipated problem may not be an Adverse Event. It is possible for an event that does not involve actual physical, psychological, social or economic harm to a research subject or another person nevertheless to constitute an unanticipated problem that must be reported to
the IRB. This is the case if the event places subjects or others at increased or different risk of harm, regardless of whether actual harm has occurred.

There are other types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at risk of harm, but no harm occurs. For example, an investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator’s care on the way home from work. This is an unanticipated problem that must be reported because the incident was (a) unexpected (i.e., the investigator did not anticipate the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of psychological and social harm from the breach of confidentiality of the study data than was previously known or recognized.

5.0 REPORTING POLICY

Investigators involved in research approved by the GHS IRB must report any event that is known by the investigator and experienced by a subject while participating in a GHS IRB approved trial that results in:

- Unanticipated problems involving risks to subjects or others that meets the criteria in 3.0;
- Death (investigators are required to report to the IRB any unexpected death of a GHS research subject within 24 hours or learning about the death; anticipated deaths (e.g. due to disease progression) must be reported at the time of continuing review);
- Hospitalization;
- Major internal protocol deviations as defined in HRPP Policy 20.0.
- New information that may affect adversely the safety of the subjects or the conduct of the clinical trial.
- Any changes significantly affecting the conduct of the clinical trial or increasing risk to subjects.

Examples of unanticipated problems that must be reported to the IRB, even though they are not adverse events, include but are not limited to:

- An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB;
- A paper is published from another study that shows that the risks or potential benefits of your research may be different than initially presented to the IRB;
- A breach of confidentiality resulting from a disclosure of confidential information or from lost or stolen confidential information, that may involve risk to that individual or others;
- Complaint of a participant or family member that indicates an unanticipated risk;
- Laboratory or medication errors that may involve potential risk to that individual or others;
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol;
- Disqualification or suspension of investigators;
- Accidental or unintentional change to the IRB-approved protocol that involves risks or has the potential to recur;
- Any unanticipated adverse device effect
- Deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant;
- Any deviation from the IRB-approved protocol that increases the risk or affects the participant’s rights, safety, or welfare;
- Incarceration of a participant in a protocol not approved to enroll prisoners;
- Event that requires prompt reporting to the sponsor.

**NOTE:** The above should be reported regardless of whether they occur during the study, after participant withdrawal or completion, or after study completion if they are profound or they demonstrate long-term risks that would necessitate notifying participants.

Investigators must follow Procedures for Reporting in Section 6.0.

### 6.0 PROCEDURES FOR REPORTING

The principal investigator will report to the GHS IRB using the eIRB Reportable Events module (see HRPP Appendices, Appendix A).

**When to Report**

**Internal Unanticipated Problems**

- A principal investigator must promptly report, by telephone, fax or email, to the IRB within 24 hours any subject death, research related hospitalization or unanticipated problem causing injury to a subject.
- All unanticipated problems that are serious adverse events must be reported to the IRB within five (5) business days of the investigator becoming aware of the event.

**Review Process for Unanticipated Problems (no greater than minimal risk)**

Investigator will notify IRB of the Unanticipated Problem via eIRB module (see HRPP Policy No. 18.0, Sect 6.0; HRPP Appendices, Appendix A). An IRB Coordinator may provide an initial review determining the risks to subjects or others. The IRB Committee Chair will subsequently review the notification and determine whether the Unanticipated Problem warrants study termination, or study suspension pending further review. The Committee Chair may solicit the Committee’s Vice Chair to additionally consider the matter. The IRB Chair will notify the investigator of their findings by filing a report in the eIRB study file.

**Review Process for Unanticipated Problems (greater than minimal risk)**

Subsequent to the investigator notifying IRB of the Unanticipated Problem via eIRB module (see HRPP Policy No. 18.0, Sect 6.0; HRPP Appendices, Appendix A), the IRB Committee Chair will review the notification and determine whether the Unanticipated Problem warrants immediate study termination, or study suspension pending further review. The Committee Chair may solicit the Committee’s Vice Chair to additionally consider the matter. The IRB Chair will present the unanticipated problem to the next convened IRB meeting (see HRPP Policy No. 18.0, Sect. 6.0, “Review by the IRB”). This presentation will include materials referenced in HRPP Policy No. 18.0, Sect 5.0. This includes, but is not limited to an interim analysis report, participant or family member complaint indicating an unanticipated risk, changes in FDA labeling, deviations from the IRB-approved protocol involving risk or potential recurrence. The committee will subsequently render a decision and course of action. The IRB Chair will notify the investigator of their findings by filing a report in the eIRB study file.
**Internal Adverse Events**

For an internal adverse event, a local investigator typically becomes aware of the event directly from the subject, another collaborating local investigator, or the subject’s healthcare provider. Upon becoming aware of an internal adverse event, the investigator should assess whether the adverse event represents an unanticipated problem following the guidelines described above (is it unexpected, related, places others at risk). If the investigator determines that the adverse event does in fact represent an unanticipated problem and requires changes to the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others, the investigator must report it to the IRB using the eIRB Reportable Events module within five (5) business days of the investigator becoming aware of the event. Unless determined to not represent an unanticipated problem by the IRB staff or the IRB Chair or Chair’s designee, the report will be reviewed at a convened IRB meeting for possible action.

*Reporting Timeframe: Five (5) business days from becoming aware of the event.*

*Note:* “No” to ANY of the 3 (unexpected, related, places others at risk) requires the PI to submit, in summary format, at the time of the next GHS IRB continuing review.

**External Adverse Events**

The majority of adverse event reports received by investigators are reports of external adverse events experienced by subjects enrolled in multicenter clinical trials. Reports of individual external adverse events often lack sufficient information to allow the investigators or the IRB at each institution engaged in a multicenter clinical trial to make meaningful judgments about whether the adverse events are unanticipated problems. As such, external adverse events should only be reported to the IRB when a determination has been made that the events meet the criteria for an unanticipated problem and requires changes to the protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others. Individual external adverse events are expected to rarely meet these criteria. Note that, in general, investigators and the IRB are not appropriately situated to assess the significance of individual external adverse events. These adverse events are better submitted for review and analysis to a monitoring entity (e.g. research sponsor, DSMB/DMC) in accordance with the monitoring plan described in the IRB approved protocol. If the external adverse event is determined to represent an unanticipated problem and requires changes to the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others, the investigator must report it to the IRB using the eIRB Reportable Events Module within five (5) business days of the investigator becoming aware of the event. Unless determined to not represent an unanticipated problem by the IRB staff or the IRB Chair or Chair’s designee, the report will be reviewed at a convened IRB meeting for possible action.

*Reporting Timeframe: Five (5) business days from notification of the event.*

**Handling non-reportable adverse events and IND safety reports**

Individual IND safety reports from external sites are generally not reportable to the IRB, because their implications for the study cannot be understood. External events should not be reported to the
IRB unless accompanied by an aggregate analysis that establishes their significance and a corrective action plan that addresses the problem.

All individual AE and IND Safety Reports shall be maintained by the investigator. For those events that are not reportable to the IRB under this policy, a summary (i.e. not individual reports) of all adverse events that have occurred within the last approval period must be submitted to the IRB at time of continuing review.

*Reporting Timeframe: Summary submitted at time of continuing review.*

Reports from a DSMB/DMC or other independent safety monitoring group should be provided to the IRB on a regular basis, generally at least as often as the study undergoes continuing review. Reports should include findings from adverse event reports and recommendations derived from data and safety monitoring.

**Review by the IRB**

If, in response to the report, the IRB chair/vice-chair conducting the review believes that immediate action is needed to ensure research subject safety, the reviewer may request that the investigator suspend research procedures or take action to suspend research procedures pending discussion of the event at the next convened meeting of the IRB. Suspension suggested by the reviewer, and in concurrence with the IRB chair/vice-chair, will follow IRB policies and procedures regarding suspensions.

Each report will have initial review by the IRB Coordinator to determine if the report may be an unanticipated problem involving risks to subjects or others.

1. All adverse events deemed to be unanticipated problems will be reported within five (5) business days of the investigator becoming aware of the event (see Section 6.0 Procedures for Reporting). All other events will be reported at the time of Continuing Review.

2. External unanticipated problems will be reviewed by the IRB Chairman or Vice-Chairman. All other external events that are submitted via the eIRB will be acknowledged by the IRB Coordinator and the PI must present a summary at Continuing Review.

IRB staff will provide the following documents to the primary reviewer:
- A copy of the event report and all attachments provided by the investigator;
- A copy of the current informed consent;
- A copy of the protocol, if requested by the reviewer; and
- Any other material that the IRB staff believes relevant to the event.

The primary reviewer will present a summary of the events and make a recommendation to the committee about whether the event represents an unanticipated problem involving risks to subjects or others. The IRB will deliberate and vote to determine whether the event requires. Examples of corrections actions or substantive changes that might need to be considered in response to an unanticipated problem and/or noncompliance include:
- No action taken, protocol continues as previously approved;
- No further action required, investigator’s proposed corrective action plan is adequate;
- Changes in informed consent documents to include a description of newly recognized risks;
- Changes in the protocol or other study documents to eliminate apparent immediate hazards to subjects;
- Modify inclusion/exclusion criteria to mitigate the newly identified risks;
- Re-consenting or informing current or previously enrolled research subjects (to occur whenever the information may relate to subjects willingness to continue participation in the research);
- Steps to reduce any immediate risks to subjects or others including withdrawal of currently enrolled participants if it is determined to be in their best interest;
- Suspension of enrollment of new subjects;
- Suspending or terminating the research study (according to the IRB policy and procedure regarding suspensions and terminations);
- Requesting more information pending final decision;
- Implementation of additional procedures for monitoring subjects;
- Refer to or consult with other organizational entities (e.g. legal counsel, risk management, institutional official, federal oversight agencies), or
- Restrict use of or destroy research data collected;
- Audit the research study(ies);
- Require additional training of the
- Modifying the continuing review schedule;
- Other actions as deemed appropriate.

As discussed in section 3.0, only a small subset of adverse events occurring in human subjects participating in research will meet these three criteria for an unanticipated problem.

7.0 ADDITIONAL REPORTING RESPONSIBILITIES

It is the Investigator’s responsibility to make all required reports of unanticipated problems or adverse events to the FDA and/or sponsor. Because the GHS IRB does not require the reporting of many adverse events, this does not obviate the investigator’s contractual relationship with sponsors or the FDA.

8.0 IRB REPORTING OF UNANTICIPATED PROBLEMS

The Medical Director, GHS Office of Human Research Protection will report unanticipated problems involving risks to participants or others to the following:
- GHS Institutional Official;
- Office for Human Research Protections
- Other federal agencies when the research is overseen by those agencies, and they require reporting separate from that to OHRP;
- FDA, when the research is FDA-regulated.

The Medical Director, GHS Office of Human Research Protection will report unanticipated problems involving risks to participants or others to the required individuals and agencies within 30 working days after the IRB’s final determination.

9.0 REQUIREMENTS FOR REPORTING ADVERSE EVENTS AT CONTINUING REVIEW

At continuing review, the GHS IRB must ensure that the criteria for IRB approval under HHS regulations at 45 CFR 46.111 and, when applicable, FDA regulations at 21 CFR 56.111, continue to be satisfied. A summary of all internal and/or external adverse events that occurred since the last continuing review must be submitted by the PI at continuing review. A summary of unanticipated problems involving risk to subjects or others that occurred since the last continuing review will be made available to the IRB reviewer by either the eIRB portal or by print out from the IRB database.
The amount of detail provided in such a summary will vary depending on the type of research being conducted.

Additionally, investigators participating in multi-center clinical trials subject to monitoring by the sponsor, a coordinating or statistical center, or a DSMB/DMC will be asked to submit a copy of the current monitoring group report/summary.

Related Policies, Regulations and References:

1. GHS OHRP Policy on Reporting Unanticipated Problems Involving Risks to Subjects of Others
2. DHHS Regulations: 45 CFR 46.113
3. FDA Regulations: 21 CFR 56.113; 21 CFR 56.113; 21 CFR 312.32(c)

10.0 ORGANIZATIONAL RESPONSIBILITIES

Any principal investigator who conducts research under the auspices of the Greenville Health System's IRB must follow this policy.

11.0 VIOLATIONS OF THIS POLICY

Failure of investigators to report events as required by this policy could result in a range of penalties determined by whether the PI has committed research misconduct pursuant to ORHP policy and procedures.
1.0 PURPOSE

The Greenville Health System Institutional Review Boards (GHS-IRBs) require disclosure to subjects of significant new findings that develop during the course of a research study, which may relate to the subject's willingness to continue participation in the research study [45 CFR 46.115(a)(7), 45 CFR 46.116(b)(5); 21 CFR 50.25(b)(5), 21 CFR 56.115(a)(7)]. Significant new findings often result in changes to the consent form or protocol after subjects have signed a consent document. The purpose of this document is to provide guidance to researchers regarding the types of information the IRB considers to constitute significant new findings, what changes to the protocol or consent form should and should not be conveyed to subjects, and the means through which the IRB expects significant new findings or changes to be conveyed to subjects.

2.0 WHAT CONSTITUTES SIGNIFICANT NEW FINDINGS REQUIRING REPORT TO SUBJECCTS

Significant new findings generally include, but are not limited to:

- Changes in potential or actual risks or benefits to subjects
  - Examples:
    - Changes in standard of care, such that participation in a research study can increase risk to subjects (i.e., subjects would be deprived of the standard of care by continuing to take part in the research study)
    - Identification of new risks to subjects currently receiving the study treatment
    - Identification of potential late-term effects for subject who completed study treatment
    - Discovery that a life threatening or severely debilitating side effect occurs more frequently than previously expected

- Addition or deletion of study procedures or change in number of visits required
  - Examples:
    - Addition of monitoring procedures
    - Addition of new instruments or questionnaires to the study
    - Collection of new or different information from subjects

- Substantive alterations to the treatment subjects expect to or currently receive
  - Examples:
    - The frequency of dosing is increased or decreased
    - The route of study drug administration is altered

- Substantive changes in potential costs or payments to subjects
  - Examples:
    - A drug previously paid for by the study funds must now be covered by insurance or the subject's personal funds
    - Payment for or costs of study participation is increased or decreased
3.0  HOW TO REPORT SIGNIFICANT NEW FINDINGS OR CHANGES TO SUBJECTS

The presentation of significant new findings to subjects can be accomplished through various means, including the following.

- A telephone call to subjects to report the significant new findings. The telephone call can be documented in the research file regarding when and who provided the new information to subjects. This method is especially encouraged when verification that subjects have received this information is needed (e.g., due to potential increased risks) and subjects are no longer being seen in person or a significant gap in time would occur between when the new findings are discovered and the next scheduled contact with the subject.
- A letter to subjects in another method that can be used to report significant new findings. This mode of communication may be suitable for information that needs to be communicated to subject when subjects are no longer seen by the researcher in person and which are not life threatening or time sensitive.
- Significant new findings or changes of protocol can be conveyed via a consent form addendum. Use of an addendum, rather than revising the consent document is particularly encouraged for subjects already enrolled in a research study and when the significant new findings is the only change that would be made to the consent document or only a few changes are proposed. Asking subjects to re-sign multiple consent forms may dilute the importance of the new information and the quality of the consent process. If a revised consent form will be used instead of an addendum, the revisions should be highlighted to draw subjects' attention to the new information.

4.0  IRB REVIEW OF SIGNIFICANT NEW FINDINGS OR CHANGES

In general, the GHS-IRBs must review the new information to be provided to subjects prior to its dissemination unless the information must be provided to subjects to eliminate an apparent immediate hazard to subjects or others. In the case where the new findings must be reported to subject before IRB approval can be obtained because of a potential immediate hazard, the researcher must report the dissemination of this information to the applicable IRB within 10 business days.

Significant new findings that the researcher proposes to disseminate can be submitted for IRB review via the eIRB Amendment module. In the case of oral dissemination of new findings, please provide the IRB a copy of the script that will be followed when contacting the subject or describe the information that will be conveyed to subjects. If subjects will be provided with written materials, these documents should be submitted with the protocol amendment.

5.0  WHEN RE-CONSENTING SUBJECTS SHOULD NOT BE PURSUED

The GHS-IRBs are aware that study sponsors often request or require researchers to present revised consent documents to subjects to sign ("re-consent") when they have been revised, regardless of the significance of the new information or change. In many cases asking subjects to sign a revised consent form is inappropriate and may result in needless burden on the subject, presentation of irrelevant information to the subjects and potential dilution of the impact of significant new findings. Consequently, the GHS-IRBs generally disallow re-consenting subjects when the revisions to consent documents would not or could not affect the subject's willingness to continue participation in the research study. Examples of situations the IRBs generally would not approve re-consenting subjects include:
• The version number or date on the consent form have been revised and no other changes have been made
• The expiration date on a consent form has been updated and no other changes have been made
• A minor increase in number of subject to be enrolled in the study
• New risk information about the study drug is discovered which are not late effects and all subject have completed study treatment
• Addition of new study procedures or additions of study visits that do not pertain to subjects already enrolled in the study (e.g., changes made to screening procedures that only affect new subjects)
1.0 SCOPE

Human subjects research deviating from the IRB policies, procedures, stipulations, decisions, state, or federal law is non-compliant. Such deviations are subject to further inquiry by the IRB and the GHS OHRP. Investigators and research staff are expected to report all non-compliance. All non-compliance reports and complaints should be directed to the GHS OHRP (via email, phone, mail, or in person). The GHS OHRP will immediately investigate all allegations of non-compliance. If necessary, (see Ethical Standards and Misconduct in Research Policy No.22.0), the GHS OHRP will notify the investigator/s in question, by registered mail, and request the immediate suspension of all specified research activities while the IRB reviews the issue of non-compliance. This policy is consistent with Federal Mandate CFR45 Part 46.113. This initial notice will also include a statement detailing the rationale for the IRB’s action. There are three categories of non-compliance: general, serious, and continuing.

Investigators are responsible for conducting human subject research in accordance with all applicable federal and state regulations, and with GHS IRB policies and procedures. During the conduct of the study, changes to the protocol may be proposed or unintentional changes may be discovered. Changes to the IRB-approved protocol, planned or otherwise, are governed by federal regulations and IRB policies and procedures. When an investigator discovers or is made aware of an unapproved deviation, s/he must report the deviation to the GHS IRB.

The federal regulations specifically require the IRB to review proposed changes in a research activity, and to ensure that such changes in approved research are not initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject 45 CFR 46.103 (b) (4)(iii) and 21 CFR 56.108 (a)(4). Research activity includes all aspects of the conduct of the research study, e.g., recruitment methods, consent process, procedures used to protect privacy and confidentiality, etc. – all of the information outlined in the protocol submission and reviewed and approved by the IRB. Non-compliance with these regulations or IRB policies and procedures during the conduct of a research study results in a protocol deviation/violation, and as such must be reported to the IRB.

Planned changes to the IRB-approved protocol must be submitted as formal protocol amendments or protocol exceptions to the IRB and must be approved prior to initiation or implementation of the change. Any changes not approved by the IRB prior to initiation are considered protocol deviations/violations, and must be reported to the IRB as outlined below.
2.0 DEFINITIONS

See Definition Section HRPP Policy No. 3.0

**Allegation of Non-compliance:** An unproven assertion of non-compliance.

**Continuing Non-compliance:** A pattern of non-compliance that indicates an inability or unwillingness to comply with the regulations or the requirements of the IRB.

**Deviation:** Any alteration/modification to the GHS IRB-approved research without prospective GHS IRB approval, The term *research* encompasses all GHS IRB approved materials and documents including the detailed protocol, protocol summary, consent form, recruitment materials, questionnaires, and any other information relating to the research study.

**Finding of Non-compliance:** Non-compliance that is true in fact. A finding of non-compliance may exist because there is clear evidence, an admission, or an investigation into an allegation has determined the allegation to be true.

**Major Deviation** Any alteration/modification to the GHS IRB-approved research that has potential to negatively impact subject safety or integrity of study data (ability to draw conclusions from the study data), or affect the subject’s willingness to participate in the study.

**Minor Deviation:** Any deviation from the GHS IRB-approved research that does not have the potential to negatively impact subject safety or integrity of study data (ability to draw conclusions from the study data), or affect subject’s willingness to participate in the study.

**Non-compliance:** Any deviation from the GHS OHRP IRB policies, procedures, or requirements and determinations, federal regulations, or state law is “non-compliance”. All non-compliance is considered misconduct. See Ethical Standards and Misconduct in Research.

**Protocol Exception:** Any temporary protocol deviation that has been approved by the IRB, the Sponsor (if applicable), and the PI prior to its initiation, (e.g., enrollment of a subject who does not meet the eligibility criteria). [Note: Any permanent change to the protocol constitutes an amendment that must be submitted to the IRB for approval prior to initiation.]

**Serious Non-compliance:** All non-compliance substantially affecting participants’ rights and/or welfare, or impacting upon the risks.

All non-compliance will be reviewed by the Medical Director, GHS Office of Human Research Protection to determine whether the allegation has a basis in fact. If there is non-compliance the Medical Director will make an initial determination on whether the non-compliance is serious and/or continuing or not. If the general non-compliance is clearly neither serious nor continuing, and there is a corrective action plan that can be readily implemented to prevent recurrence, then the matter may be filed and no further action is needed (for example, failure to sign the application or lost consent forms). Otherwise, the GHS OHRP Medical Director will refer allegations and findings of non-compliance to undergo an evaluation by an IRB sub-committee.

The IRB sub-committee will be comprised of two members of the IRB and one staff member of the GHS OHRP. This sub-committee will review the nature of the non-compliance and complete the non-compliance form (Appendix C). The IRB sub-committee will make a recommendation to the IRB that includes whether the non-compliance is serious or continuing and a course of action, such as:
- Modifying the research protocol;
- Modifying the consent process;
- Contacting past or current participants with additional information (for current participants whenever that information might affect their willingness to continue to take part in the research);
- Re-consenting participants;
- Modifying the approval period;
- Suspension;
- Termination;
- Utilizing the Peer Review Process.

The IRB will review the recommendation of the IRB sub-committee at a convened meeting. All IRB members will be provided with a copy of the approved protocol, current consent documents, and the report of the IRB sub-committee with any supporting documents. A member of the IRB sub-committee will serve as a primary reviewer. The relevant IRB files, if any, will be made available at the IRB meeting. The IRB may accept or reject the sub-committee’s recommendations. If the IRB rejects the sub-committee’s recommendation then the IRB may modify the recommendation for successful resolution described by the IRB sub-committee. The IRB will assess and vote upon whether any allegations of non-compliance were true, and whether any findings of non-compliance were serious or continuing. If necessary, the IRB may request additional information before issuing determinations. The IRB reserves the right to request any appropriate additional consultation and expertise to resolve non-compliance.

3.0 REPORTING REQUIREMENTS

When an investigator discovers or is made aware of an unapproved deviation, s/he must report the deviation to the GHS IRB as an unanticipated problem as follows:

1. Unapproved major deviations must be reported to the GHS IRB within five (5) working days of the date the investigator becomes aware of the unapproved deviation.

2. Unapproved minor deviations are to be recorded by the investigator in a protocol-specific Minor Deviation Log and submitted to the GHS IRB at continuing review. For research limited to the use of medical records or excess human material, in lieu of a Minor Deviation Log, unapproved minor deviations may be described in the eIRB, General Comments section of the continuing review module.

Unapproved deviations should be reported to the sponsor as outlined in the sponsor’s protocol or research or investigative plan.

It is the responsibility of the Principal Investigator (PI) to determine whether an unapproved deviation from the GHS IRB-approved protocol is major or minor and to ensure proper reporting to the GHS IRB. When making the determination of whether the unapproved deviation is major or minor, the Principal Investigator should consider whether the deviation negatively affected any of the following:
- The rights or welfare of the subject;
- Risk benefit assessment;
- The integrity of the data (ability to draw conclusions from the study data)
The Principal Investigator (PI) is responsible for reviewing the Minor Deviation Log periodically to monitor compliance with the approved research. Frequent minor deviations of a similar nature should be reported to the GHS IRB as a major deviation.

Reports of all protocol deviations/violations should be submitted to the sponsor as outlined in the sponsor’s protocol.

**Major Deviations** *(the list of examples is intended as a guide and is not all-inclusive)*

- Changes necessary to eliminate apparent immediate hazards to the subject;
- Failure to obtain informed consent (i.e. there is no documentation of informed consent).
  - Informed consent obtained after initiation of study procedures
- Informed consent for IND/IDE studies obtained by someone other than individuals authorized by IRB to obtain consent (e.g. someone other than a licensed physician investigator)
- Enrollment of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the IRB
- Failure to report a serious adverse event to the IRB and/or sponsor
- Failure to perform a required lab test that, in the opinion of the PI, may affect subject safety or data integrity
- Study visit conducted outside of required timeframe that may affect subject safety
- Failure to follow safety monitoring plan
- Evidence of coercion

**Minor Deviations** *(the list of examples is intended as a guide and is not all-inclusive)*

- Implementation of unapproved recruitment procedures
- Missing original signed and dated consent form (only a photocopy available)
- Missing pages of executed consent form
- Inappropriate documentation of informed consent, including
  - Failure to follow the approved study procedure that, in the opinion of the PI, does not affect the subject safety or data integrity.
  - Study procedure conducted out of sequence
  - Omitting an approved portion of the protocol
  - Failure to perform a required lab test
  - Missing lab results
- Failure of subject to return study medication
- Over-enrollment
- Enrollment of subjects after IRB-approval of study expired
- Failure to submit continuing review application to the IRB before study expiration

### 4.0 DISCREPANCIES IN APPLICATION OF POLICIES OR REGULATIONS

The IRB plays a central role in reconciling non-willful discrepancies in the application of policies or regulations. When such discrepancies are discovered, an inquiry into the situation is initiated. This inquiry is reviewed by the Chairperson, or Vice-Chairperson. The inquiry may include a meeting with the investigator. A corrective action plan is developed and presented to the IRB for discussion and ratification. Revisions to the plan are made as needed. The final plan is then presented and approved by the IRB prior to allowing the investigator to apply the corrective action plan.

### 5.0 GHS OHRP REPORTING REQUIREMENTS
The Medical Director, GHS Office of Human Research Protection will report serious and continuing non-compliance to regulatory agencies, and appropriate organizational officials. Reports will be made to:

- Institutional Official, Greenville Health System;
- OHRP when the research is covered by DHHS regulations;
- Other federal agencies when the research is overseen by those agencies, and they require reporting separate from the OHRP;
- FDA, when research is FDA-regulated.

The Medical Director, Office of Human Research Protection (OHRP) will make the required reports within thirty (30) working days of the final IRB decision.
1.0 PURPOSE

The purpose of this policy is to define the procedures the GHS Office of Human Research Protection Institutional Review Board (IRB) follow when suspending or terminating IRB-approved human subjects research and clinical investigations.

This policy is established to comply with the regulatory requirements in 45 CFR 46.103(b)(5)(ii) and 21 CFR 56.108(b)(3) requiring IRBs to have written procedures ensuring prompt reporting to the Institutional Official, Office for Human Research Protections (OHRP), and when applicable, the Food and Drug Administration (FDA), any suspension or termination of IRB approval.

2.0 SCOPE

Non-exempt human subjects research and clinical investigations approved by the GHS IRB are subject to this policy.

3.0 DEFINITIONS

Suspension means to cause some aspect of the research to be stopped temporarily or permanently while the research continues under review or an investigation takes place.

Termination means to cause the research to be stopped permanently in its entirety. Expiration of IRB approval is not considered termination of research.

Administrative Hold is an investigator-initiated request to temporarily or permanently stop all approved research activities, including enrollment. An administrative hold does not apply/may not be used to address interruptions related to safety, rights, or welfare of human research participants, investigators, staff, or others.

4.0 POLICY

Suspension or Termination

Consistent with federal regulations, the GHS IRB is authorized to suspend or terminate approval of research violating the requirements or determinations of the IRB, or that is associated with unexpected serious harm to subjects. Additionally, the Institutional Official may suspend or terminate research approved by the IRB for human subject protection, administrative, financial or other reasons.
When the Institutional Official (IO) suspends or terminates IRB-approved research, the IO is responsible for promptly notifying the Principal Investigator, Department Chair and the IRB that the research was suspended or terminated and the reason for doing so.

When the IRB suspends or terminates approved research, the IRB is responsible for promptly reporting the suspension or termination and providing an explanation.

**Administrative Hold**

GHS OHRP IRB may grant a principal investigator’s request for an administrative hold. An administrative hold must not be used to avoid reporting deficiencies, or circumstances that otherwise require reporting regulatory agencies. Activities placed under administrative hold remain subject to continuing review and all organizational policies (including, but not limited to, HRPP Policy No. 18.0; HRPP Policy No. 22.0). Investigators may not request an administrative hold during a study audit. An administrative hold cannot be used to extend IRB approval beyond the expiration date of a protocol without IRB approval of continuing review. GHS IRB may grant an administrative hold when the principal investigator is challenged to dutifully ensure research conduct consistent with the IRB-approved protocol. Examples include investigator sabbatical or leave of absence.

**5.0 PROCEDURES**

**Suspension or Termination**

5.1 When research approved by the IRB is suspended or terminated, the IRB Chairperson/IRB considers and determines whether:
   - Subjects currently on active treatment must be withdrawn from the study;
   - Subjects will be placed at risk of harm by withdrawing them from the study; and
   - Subjects must continue to be followed for safety reasons.

5.2 Early Withdrawal of Subjects

5.2.1 When the suspension or termination involves withdrawal of subjects from an interventional study, the IRB Chairperson/IRB considers and determines what, if any, termination procedures are required for the safety and welfare of those subjects. Termination procedures may include, but are not limited to the following:
   - Tapering of the drug;
   - Making a final study visit at which a physical exam and/or laboratory or other tests will be performed; or
   - Making arrangements for subjects to receive medical care by their primary care physician or specialist or through referrals to other healthcare providers.

5.3 When Subjects are at Risk of Harm

5.3.1 When the IRB determines that the suspension or termination will place subjects at risk of harm, the IRB must determine what subjects are to be told and the manner in which they are to be notified (e.g., in writing, in person, or by telephone).

5.4 Subject Follow-Up

5.4.1 When the IRB requires or approves subject follow-up for safety reasons, the investigator is subject to continuing review and requirement to promptly report any
unanticipated problems involving risks to subjects or others, including adverse events, to the IRB and, when applicable, the sponsor.

5.5 Notification of Subjects

5.5.1 Depending upon the reasons for the suspension or termination and the design of the protocol, the IRB may require that the following subjects be notified of the suspension or termination:

- All subjects who have been or are enrolled;
- Subjects currently on protocol; or
- Subjects who participated in a certain aspect of the protocol.

5.6 Reporting Requirements

When the Institutional Official or IRB suspends or terminates a research protocol involving human subjects, the GHS OHRP Medical Director and IRB Chair, or designee, shall be responsible for submitting a report of the suspension or termination of the research to the following:

- GHS Institutional Official, if suspended and terminated by the IRB;
- GHS Chief of Medical Staff Services, if applicable;
- Office for Human Research Protections;
- Other federal agencies when the research is overseen by those agencies, and they require reporting separate from that of OHRP;
- FDA, the research is FDA-regulated.

Reports shall be submitted within thirty (30) days of the suspension/termination by the Institutional Official or IRB.

Administrative Hold

The principal investigator will submit a letter (via eIRB) requesting GHS ORHP IRB grant administrative hold. The letter will include protocol number, study title, and principal investigator signature. The letter will provide a rationale or note circumstances mandating the administrative hold. The letter will include a projected request for administrative hold release. However, a projected hold release is for information purposes only. An investigator may NOT resume a study until the principal investigator submits an administrative hold release request, and IRB approves the request.

An IRB Coordinator will forward the letter to the IRB Chair for consideration. The IRB chair may grant a hold, and notify the principal investigator via eIRB. The IRB Coordinator will also note the projected hold release in the eIRB and reference the letter and Chair approval in continuing reviews.

Principal investigator request for administrative hold release will be submitted in writing (via eIRB). The letter will include protocol number, study title, and principal investigator signature. An IRB Coordinator will forward the letter to the IRB Chair for consideration. The IRB Chair may release the hold, and allow the study to resume as outlined in the IRB-approved application/protocol.
1.0 PURPOSE

OHRP and IRB will not condone any compromise of the ethical standards required for conducting research. Breaches in such standards are rare; when breaches occur, all parties must address the breaches promptly and fairly to preserve the integrity of the research community.

2.0 DEFINITION

Research Misconduct, as used herein, includes intentional, reckless or negligent failure to abide by applicable laws, regulations, or IRB procedures; intentional, reckless or negligent misuse of patient information; plagiarism; fabrication or intentional falsification of data, research procedures or data analysis; or other deliberate misrepresentation in proposing, conducting, reporting, or reviewing research. It does not include honest error or honest differences in interpretations or judgments of data. In cases of allegations involving activities submitted to or supported by a federal agency, the definition for misconduct specified in the agency’s regulations will apply.

3.0 ADDRESS OF MISCONDUCT CONCERNS

A. Concerns about potential misconduct by any individual engaged in research (“Researcher”), should be communicated immediately to the Office of Human Research Protection. Allegations of misconduct should be submitted in writing so that a systematic inquiry can be undertaken. The confidentiality of the individual making the report will be protected to the extent, reasonably possible for those who in good faith report apparent suspected misconduct.

B. The IRB Chair will make a preliminary inquiry or appoint someone to make a preliminary inquiry the allegation. The Chair or appointee will determine whether there are sufficient grounds for valid accusation. The Chairperson may request legal counsel to coordinate the inquiry. During this inquiry, the IRB Chair or designee will consult the accused, and provide the accused an opportunity to respond to the allegations. The IRB Chair (or designee) will expedite the inquiry, and in no event shall the inquiry process exceed 30 days.

C. The Chairperson will make a report to the IRB regarding the preliminary inquiry. The Chairperson may call a special meeting for the purpose of making this report. The IRB will determine whether, in its sole discretion, further investigation is necessary. If not, the IRB minutes will include an explanation of why the allegations do not warrant further investigation or corrective action.

If the IRB determines that further investigation is warranted, it shall appoint a sub-committee to examine and evaluate relevant facts to determine whether misconduct has taken place. The
investigative sub-committee should include at least three (3) members of the Institutional Review Committee. Other members may be appointed to obtain necessary expertise. Precautions against real or apparent conflict of interest will be taken in appointing the sub-committee. The IRB may request that legal counsel coordinate the sub-committee investigation.

The IRB may take interim administrative action based on the allegations and preliminary inquiry, prior to completion of the investigation if such action is deemed appropriate by the IRB, in its sole discretion, to reduce risks to research participants. These steps may include supervision or suspension of a research study or other appropriate action.

D. At the time the sub-committee is appointed, the Chairperson of the IRB shall inform in writing the individual(s) about whom allegations have been made and any involved collaborators that an investigation is to be conducted and shall present to them a statement of the allegations. This statement shall include information on the nature of the allegations and the focus of the investigation and shall inform those being investigated of the opportunity to defend their conduct and provide comment and other relevant information to the committee and consult with legal counsel if desired.

E. The sub-committee shall examine and evaluate the relevant facts to determine if the allegations of misconduct are valid. The sub-committee may call witnesses, examine research data (both published and unpublished), and seek expert counsel both inside and outside of the Institution to aid in the investigation. The sub-committee will prepare a summary of each interview conducted, and a copy shall be provided to the interviewed party for comment or revision. The sub-committee will keep the IRB apprised of the investigation.

The sub-committee shall complete its investigation, including submission of the final report, in the shortest feasible period of time but not later than 120 calendar days. If the sub-committee is unable to complete the investigation in 120 days, a request for extension, which includes an explanation for the delay, must be submitted to and approved by the Chairperson of the IRB.

F. At the completion of the investigation, the sub-committee shall submit its findings and recommendations in writing to the IRB, who will provide a copy to the individuals being investigated. All those being investigated shall be afforded the opportunity to comment upon the report and have comments included in the formal records of the investigation. The person who raised the allegations will be provided with those portions of the report that address his/her role and opinions in the investigation, and his/her comments, if any, shall be included in the formal record as well. All parties involved in the investigation shall strive to maintain confidentiality of this information.

If the sub-committee has reason to believe that unfounded charges have been brought with malicious or dishonest intent, the sub-committee should recommend consideration of appropriate administrative action.

G. The IRB will accept or reject the sub-committee’s recommendations. The IRB may require further investigation before taking final action.
If the IRB determines that the sub-committee’s findings fail to confirm an instance of misconduct, participants in the investigation shall be so informed in writing by the Chairperson of the IRB.

H. If the IRB determines that based on the sub-committee’s findings, Research Misconduct has occurred, it shall take the following action:

1. Appropriate administrative actions will be taken against those directly involved in the Research Misconduct, including restriction on their involvement in research at GHS or relying institution.

2. Appropriate entities will be notified of the findings, including governmental agencies, sponsors, the GHS Medical Staff, and GHS administrators, or the administration of a relying institution.

3. If required by a governmental agency or sponsor, a written assurance will be submitted that GHS is in compliance with requirements for handling allegations of Research Misconduct.

4. Appropriate steps will be taken to protect or minimize risk to research subjects, including but not limited to suspension or termination of a research study.

5. Publishers and editors of journals shall be informed that manuscripts emanating from Research Misconduct have been submitted or published.

I. No administrative action taken pursuant to this policy shall affect a Researcher’s Medical Staff privileges at GHS. However, a report may be made by the IRB to the Medical Staff Officers for consideration under the Medical Staff’s own Bylaws.
1.0 SCOPE

Investigational drugs, devices or procedures shall not be used without prior approval of the IRB. Such use must be reviewed in advance at a regularly scheduled meeting of the IRB, except for emergency (please refer to Section entitled “Emergency Use Notification and Reporting”).

Only the PI, or Co-investigator under the direction and supervision of the PI shall use investigational drugs, devices, or procedures. The PI and any other Co-investigators must be active members of the GHS Medical Staff (or the institution approving the study), qualified to do research, and must be approved by the IRB.

IRB will provide the investigator written approval for investigational drugs, devices or procedure use. If the IRB disapproves the protocol, the IRB will provide a written notification noting decision rationale, and allow the investigator to provide the committee a response in person or in writing.

2.0 RESEARCH INVOLVING AN INVESTIGATIONAL DRUG OR DEVICE

The following information applies to PIs and to PIs who may also be sponsors holding an Investigational New Drug (IND) or Investigational Device Exemption (IDE) for the test article under study.

1. When the principal intent of the investigational use of a test article is to develop information about the product’s safety or efficacy, an IND or IDE may be required. The decision for a test article to be considered an exemption may only be made by the Greenville Health System OHRP Medical Director. When the research requires an IND or an IDE, it is the investigator’s responsibility to submit the appropriate application to the FDA, obtain the necessary documentation, and provide this document to the IRB as a part of the approval process. The research must not begin until a valid IND or IDE, whose IND or IDE number validity is confirmed by the Greenville Health System OHRP Medical Director, is in effect. This includes recruiting, obtaining consent, and screening subjects for a specific study that is required of the IND or IDE. The IND goes into effect 30 days after the FDA receives the IND unless the sponsor receives earlier notice from the FDA.

   a. When research is conducted to determine the safety or effectiveness or a device it must fulfill all of the following requirements: (a) the device is not a banned device; (b) the sponsor labels the device in accordance with 21 CFR 812.5.; (c) the sponsor
complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations.

b. An IND may not be necessary if all of the conditions stated in 21 CFR 312.2(b)(1) have been met. If the PI does not already have an IND, the PI will be notified that IRB approval is pending receipt of an IND. If there is a debate regarding the need for an IND, the IRB will require that the PI contact the Food and Drug Administration (FDA) to obtain written documentation that an IND is not necessary.

c. The IRB will review protocols involving investigational devices to determine if the device is a “Significant-Risk device” (SR) or a “Non-Significant Risk” (NSR) device. If the IRB determines that the research involves a SR device, an IDE is necessary. If the PI does not already have an IDE, the PI will be notified electronically that IRB approval is pending receipt of an IDE.

2. Protocols involving an Investigational Drug (IND) or Investigational Device (IDE) require consideration and satisfaction of the pertinent FDA and the DHHS regulations (21 CFR 50, 21 CFR 56, 21 CFR 312, 21 CFR 812, and 45 CFR 46). When the GHS PI is acting as the sponsor of research involving an investigational drug, the IRB requires that the PI submit documentation that the proposed drug preparation has been reviewed and compliance with Current Good Manufacturing Practices has been confirmed. In addition, when a GHS PI is acting as the sponsor of research involving an investigational drug or device, the IRB requires that the PI review the reporting and record-keeping responsibilities as stated in 21 CFR 312 and 21 CFR 314 (for investigational drugs) or 21 CFR 812 and 21 CFR 814 (for investigational devices).

3. The PI is responsible for assuring the IRB that investigational drugs and devices are stored in a secure and safe manner and that the storage and safety requirements are consistent with FDA, sponsor, and affiliated research institutions’ storage requirements for drugs or devices of the type under study. Whenever possible, the storage of drugs and biologics should be under the supervision of a registered pharmacist and stored in the pharmacy in a limited access, locked area. Devices should be stored according to manufacturer’s specifications and maintained in a limited access area. Access to the test devices must be limited only to those authorized to use the devices.

4. The PI is responsible for ensuring that test articles (drugs, biologics, or devices) are controlled so that they are not used outside of a research study. An investigator shall administer the drug or device only to subjects under the PI’s personal supervision or under the supervision of a sub-PI responsible to the PI. The PI shall not supply the investigational drug or device to any person not authorized under this part to receive it.

5. The protocol for the study should outline the security and storage plan for the test article(s) indicating that the plan meets the sponsor’s storage and security requirements. The plan should include whether or not control will be through a hospital pharmacy and under the supervision of a registered pharmacist or held in a proper and secure storage area by the investigator. The protocol should detail how the test article is used in human subjects, indicate who may have access to the test article(s) and outline the accountability plan for the test article(s) to ensure that there is no unapproved access to or use of the test article(s).

6. A PI who is also a sponsor shall select a monitor qualified by training and experience to
monitor the progress of the investigation.

7. Protocols involving an IND or IDE will undergo initial and continuing review at a convened meeting that includes at least one physician or pharmacist unless the protocol meets the criteria for expedited review (i.e., all treatment components complete, in follow-up only, data analysis only).

8. For studies using investigational drugs or devices, an Investigator’s Brochure and a copy of the IND or IDE letter from the FDA must be submitted to the IRB for review. When the Investigator’s Brochure is revised by the sponsor, it is the responsibility of the investigator to submit the revised document to the IRB. This submission should include a summary of the changes.

9. Consent for studies involving an IND and/or IDE will be obtained. Although FDA regulations allow waiver of consent if research meets the criteria specified in 21 CFR 50.23 or 21 CFR 50.24 and DHHS regulations allow a waiver of consent if research meets the criteria specified in 45 CFR 46 and 45 CFR 46 “Waiver of Informed Consent Requirements in Certain Emergency Research,” consent is required for all non-emergency research that falls under FDA regulations or involves experimental treatment, tests, or drugs. In addition, the consent form will identify the test article as investigational and will inform participants that the FDA may inspect research records.

10. The PI who is a sponsor will provide the IRB with all documentation provided by the FDA indicating whether or not the sponsor has complied with FDA regulations dealing with sponsor responsibilities.

11. In addition to this documentation, the IRB, utilizing the GHS auditors, will ensure through a focus audit of the production and storage area for the test article that the sponsor/investigator has met all the sponsor responsibilities as detailed in 21 CFR 312 for drugs or biologics and 21 CFR 812 for test devices.

12. The OHRP must be notified of participants who are enrolled in a research study at another institution and come to this institution for part of their treatment before treatment may begin. A copy of the signed consent form must be brought with the patient and placed on the patient’s chart before treatment begins.

13. The PI/sponsor will provide the IRB with a final report at the close of the study (PI must file a Study Closure Notice).

14. Where allowed or required, the investigator may assign some or all duties for investigational articles accountability at the trial sites to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator.

15. The investigator, pharmacist, or other designated individual will maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused products. These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial subjects.

16. Investigators should maintain records that document adequately that the subjects are
provided the doses specified by the protocol and reconcile all investigational products received from the sponsor.

2.1 **Determining if the Study Qualifies for Exemption from the Requirement to have an IDE:**

- The device fulfills one of the IDE exemption categories:
  - A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
  - A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under Subpart E or Part 807 in determining equivalence.
  - A diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809..10(c) and if the testing:
    - Is non-invasive.
    - Does not require an invasive sampling procedure that presents significant risk.
    - Does not by design or intention introduce energy into a subject.
    - 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.

2.2 **Documentation of Need for an IND**

Studies that involve FDA-regulated products that are submitted without a valid IND number will be reviewed with respect to determining the need for an IND, based on the investigator’s response to questions contained in the application form.

If the IRB determines that the study is exempt from an IND and approves the study, the study may begin without submission of an IND application to the FDA. If the IRB determines that an IND is needed, the investigator/sponsor must submit an IND application to the FDA and provide documentation of the outcome of the FDA determination (IND number) to the IRB before the IRB approves the study.

The IRB may consider a study using a drug product that is lawfully marketed in the United States to be exempt from the requirements for obtaining an IND if all the following apply:

1. 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 changes in the labeling for the drug;

2. 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;

3. The investigation does not involve a route of administration or dosage level or use in a patient population (e.g., children, prisoners, pregnant women and fetuses) or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

4. The investigation is conducted in compliance with the requirements for institutional review and with the requirements for informed consent; and

5. The investigation is conducted in compliance with the requirements with regard to promotion and charging for investigational drugs in 21 CFR 312.7.

A clinical investigation involving an in vitro diagnostic biological product that is a blood grouping serum, reagent red blood cells, or anti-human globulin is exempt from the requirements that an IND if (a) it is intended to be used in diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (b) it is shipped in compliance with 21 CFR 312.160.

A drug intended solely for tests in vitro is exempt from the requirements of an IND if it is shipped in accordance with 21 CFR 312.160.

A clinical investigation involving use of a placebo is exempt from the requirements of an IND if the investigation does not otherwise require submission of an IND.

2.3 Determination of Significant Risk (SR) vs. Non-significant Risk (NSR) for Non-Exempt Medical Devices

For determination of the need for an IDE, the convened IRB will address the applicability of FDA regulations under 21 CFR.812.2 and, if necessary, make a significant risk determination.

A Significant Risk (SR) Device study is one that presents a potential for serious risk to the health, safety, or welfare of a subject and

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

A Non-significant Risk (NSR) Device investigation is one that does not meet the definition for a SR study.
The risk determination is based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses an SR, the IRB considers the nature of the harm that may result from use of the device. Studies where the potential harm to subjects could be life threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure is considered SR. Also, if the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB considers the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

FDA has the ultimate decision in determining if a device study is SR or NSR.

If an investigator or a sponsor proposes the initiation of a claimed NSR investigation to an IRB, and if the IRB agrees that the device is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA.

To help in the determination of the risk status of the device, an investigator is asked to include the sponsor's (including the investigator or investigator-initiated studies) assessment of whether or not a device study presents a significant or non-significant risk. The investigator must provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. The investigator must inform the IRB whether other IRBs have reviewed the proposed study and what determination was made. The investigator must inform the IRB of the FDA’s assessment of the device’s risk if such an assessment has been made. The IRB may also consult with FDA for its opinion.

### 3.0 RESPONSIBILITIES OF AN INVESTIGATOR WHO IS ALSO ACTING AS A SPONSOR FOR SIGNIFICANT RISK DEVICE INVESTIGATIONS

This section is intended to assist investigators (hereafter referred to as sponsors) who are also sponsors in identifying and complying with their responsibilities in connection with the conduct of clinical investigations of medical devices that are deemed “significant risk” by the reviewing IRB or by FDA. For a complete description of their responsibilities, sponsors should refer to the actual text of the regulations cited below. In addition, sponsors should be aware that a clinical investigation must be conducted in accordance with any requirements imposed by the reviewing IRB, by institutional policies, or by state law.

#### 3.1 General Duties

1. Submitting an IDE application to FDA;
2. Obtaining both FDA and IRB approvals for the investigation and submitting certification of IRB approval to FDA before shipping the device to any investigator;
3. Obtaining FDA approval and IRB approval for a supplemental application before beginning that portion of the investigation;
4. Selecting qualified investigators;
5. Ensuring proper monitoring;
6. Ensuring patient informed consent is obtained.

#### 3.2 Selection of Investigators
1. Assuring selection of investigators qualified by training and experience;
2. Shipping the investigational device only to participating investigators;
3. Obtaining a signed investigator’s agreement containing:
   a. investigator’s curriculum vitae;
   b. statement of investigator’s relevant experience, including dates, location, extent, and type of experience;
   c. if an investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that lead to the termination;
   d. statement of the investigator’s commitment to:
      I. conduct the investigation in accordance with the agreement, the investigational plan, Parts 50, 56, and 812, and any conditions of approval imposed by the IRB or FDA;
      II. supervise all testing of the device involving human subjects;
      III. ensure that the requirements for informed consent are met (21 CFR Part 50)
4. Providing investigators with the necessary information to conduct the investigation including, but not necessarily limited to:
   a. the investigational plan;
   b. the report of prior investigations.

3.3 Monitoring

Selecting monitor(s) qualified by training and experience to monitor the progress of the investigation;

1. Securing compliance of all investigators in accordance with the signed investigator’s agreement, the investigational plan, the requirements of this part or other applicable FDA regulations, or any condition of approval imposed by the reviewing IRB or FDA. If compliance cannot be secured, shipment of the device to the investigator and the investigator’s participation in the investigation must be discontinued;
2. Ensuring that significant new information about the investigation is provided to all reviewing IRB’s, FDA, and investigators;
3. Evaluating all unanticipated adverse device effects and terminating the investigation, or portions of it, if that effect presents an unreasonable risk to subjects (reporting requirements are listed below.)
4. Resuming terminated investigations only after both FDA and IRB approvals are obtained.

3.4 Controlling Distribution and Disposition of Devices

Although investigators are responsible for ensuring that investigational devices are made available only to persons who are legally authorized to receive them (see 21 CFR 812.110(c)), sponsors also bear responsibility for taking proper measures to ensure that devices are not diverted outside of legally authorized channels. Sponsors may ship investigational devices only to qualified investigators participating in the clinical investigation (§ 812.43(b)). Sponsors must also maintain complete, current, and accurate records pertaining to the shipment and disposition of the investigational device (§ 812.40(b)). Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of disposition shall describe the batch number or code marks of any devices returned to the sponsor, repaired, or
disposed of in other ways by the investigator or other person, and the reason for and method of disposal.

To further ensure compliance with these requirements, sponsors should take appropriate measures to instruct investigators regarding their responsibilities with respect to recordkeeping and device disposition. The specific recordkeeping requirements for investigators are set forth at § 812.140(a). Upon completion or termination of a clinical investigation (or the investigator’s part of an investigation), or at the sponsor’s request, an investigator is required to return to the sponsor any remaining supply of the device or otherwise to dispose of the device as the sponsor directs (§ 812.110(c)).

3.5 Prohibition of Promotion and Other Practices (21 CFR 812.7)

The IDE regulations prohibit the promotion and commercialization of a device that has not been first cleared or approved for marketing by the FDA. This prohibition is applicable to sponsors and investigators (or any person acting on behalf of a sponsor or investigator), and encompasses the following activities:

1. Promotion or test marketing of the investigational device;
2. Charging subjects or investigators for the device a price larger than is necessary to recover the costs of manufacture, research, development, and handling;
3. Prolonging an investigation beyond the point needed to collect data required to determine whether the device is safe and effective; and,
4. Representing that the device is safe or effective for the purposes for which it is being investigated.

3.6 Supplemental Applications

Supplemental applications are required to be submitted to, and approved by, FDA in the following situations:

1. Changes in the investigational plan: FDA approval is required for any change that may affect the scientific soundness of the investigation or the rights, safety or welfare of the subjects. IRB approval is also required for changes that may affect the rights, safety or welfare of the subjects. The change in the investigational plan may not be implemented until FDA approval (and IRB approval, if required) is obtained.
2. Addition of new institutions: IRB approval is also required for new institutions. The investigation at the new institution(s) may not begin until both FDA and IRB approval(s) are obtained, and certification of IRB approval is submitted to the FDA.

3.7 Maintaining Records

A sponsor shall maintain the following accurate, complete, and current records relating to an investigation:

1. Correspondence with another sponsor, monitor, investigators, an IRB or FDA
2. Records of shipment, including:
   a. name and address of consignee
   b. type and quantity of device
   c. date of shipment
   d. batch numbers or code marks
3. Records of disposition, describing:
   a. batch number or code mark of devices returned, repaired, or disposed of
3.8 Submitting Reports

A sponsor shall prepare and submit the following complete, accurate, and timely reports to the FDA, Investigator(s) and/or appropriate IRB:

1. Unanticipated adverse device effects (with evaluation) to FDA, appropriate IRB(s) and investigators within 5 working days after notification by the investigator. Subsequent reports on the effect may be required by FDA.
2. Withdrawal of IRB approval.
3. Withdrawal of FDA approval.
4. Current 6 month investigator list.
5. Annual progress report.
6. Recall and device disposition (within 30 working days after the request was made).
7. Final report.
8. Use of device without obtaining patient informed consent.
9. Significant risk determinations by the IRB when proposed to be nonsignificant risk.
10. Other reports requested by the IRB or FDA.

3.9 Inspections

Sponsors are required to permit FDA to enter and inspect (at reasonable times and in a reasonable manner) any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records or results from use of devices are kept). FDA may also inspect and copy all records relating to an investigation including, in certain situations, records that identify subjects.

The IRB may agree or disagree with the investigator/sponsor’s initial NSR assessment. If the IRB agrees with the sponsor’s initial NSR assessment and approves the study, the study may begin without submission of an IDE application to the FDA. If the IRB disagrees, the sponsor should notify the FDA that an SR determination has been made and the initiation of the study must be delayed until the FDA approval of an IDE application has been granted.

If the IRB decides the device/study is significant risk, it notifies the investigator of this decision. The IRB must be provided with notice that an IDE has been granted, and the IDE number must appear on the investigator’s IRB application prior to final full board review.

Once the SR/NSR decision has been reached and proper documentation provided, the IRB considers whether the study should be approved or not. Full IRB review is required for all studies involving investigational devices. The criteria for deciding if SR and NSR studies are approved are the same as for any other study. Minutes of IRB meetings document the rationale for SR/NSR and subsequent approval or disapproval decisions for the clinical investigation.

4.0 DEVICE STUDIES IN PEDIATRIC POPULATIONS
Because the pediatric population represents a particularly vulnerable group, specific measures are needed to protect the safety of pediatric study subjects. Adult devices may be inappropriate for use in pediatric subjects for a variety of reasons, or may require specific design changes and/or specific labeling to accommodate their use in pediatric subjects. IRB recommends that the following be considered in clinical trials for devices intended for pediatric subjects:

1. height;
2. weight;
3. growth and development;
4. disease or condition;
5. hormonal influences;
6. anatomical and physiological differences from the adult population;
7. activity and maturity level;
8. immune status.

4.1 Pediatric Subgroups

If clinical data are needed to support a pediatric indication, the investigator should make every effort to compile data that adequately addresses each targeted pediatric subgroup. In some cases, the expected benefit and safety can be determined without separate studies in each subgroup. In other cases, such as with neonates, it may be necessary to collect clinical data for that specific subgroup.

Please review the FDA publication *Premarket Assessment of Pediatric Medical Devices* for additional information about research involving pediatric medical devices.

5.0 TREATMENT USE OF AN INVESTIGATIONAL DRUG OR DEVICE

The IRB reviews the use of investigational drugs/devices if the investigator provides evidence that a treatment IND or IDE has been obtained or as single patient use (below). In all cases, treatment use of an investigational drug or device requires prospective IRB approval as well as subject informed consent.

5.1 Single Patient (Non-emergency Use)

In non-emergency situations, physicians may obtain investigational drugs for use outside a controlled clinical trial for a single patient. This is often referred to as “compassionate use.” Usually the patient is in a desperate situation and unresponsive to other therapies, or no approve or generally recognized treatment is available. There may be little evidence that the proposed therapy is useful, but it is thought to be plausible on theoretical grounds or anecdotal evidence. Access to investigational drugs for use by a single, identified patient may be gained either through the sponsor and then submitting a treatment IND to the FDA requesting authorization to use the investigational drug for treatment.

IRB approval is also required prior to administration of the investigational drug. The approval is granted for the treatment of a single patient. When an investigator desires to obtain single patient use approval, the investigator submits an application and the study is assigned a GHS eIRB number and sent through the new application procedure. The treatment use may occur only after IRB approval is obtained. Subsequent treatment uses require FDA approval for a treatment IND or IDE.
Every single patient use must be reviewed and approved by the IRB as well as the FDA, and all requirements for informed consent must be met. Although the FDA may waive local IRB review for a Single Patient Use, the GHS IRB policy does not permit such waivers and will not allow a Single Patient use without the prior review and approval of the IRB.

5.2 Humanitarian Use Device (HUD)

Humanitarian use of investigational devices is prospectively reviewed by the IRB. The investigator is required to submit a new application for review. Included in the application must be evidence that the investigator/sponsor has obtained a Humanitarian Device Exemption (HDE) from the FDA. These projects are subject to the same new and continuing review requirements as research projects as outlined in these policies. The use of such devices is approved only for the purposes noted in the FDA approval letter.

5.3 Treatment IND

The treatment IND [21 CFR 312.34 and 312.35] is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug “may be effective” and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

5.4 Group C Treatment IND

The “Group C” treatment IND was established by agreement between FDA and the National Cancer Institute (NCI). The Group C program is a means for the distribution of investigational agents to oncologists for the treatment of cancer under protocols outside the controlled clinical trial. Group C drugs are generally Phase 3 study drugs that have shown evidence of relative and reproducible efficacy in a specific tumor type. They can generally be administered by properly trained physicians without the need for specialized supportive care facilities. Group C drugs are distributed only by the National Institutes of Health under NCI protocols. Although treatment is the primary objective and patients treated under Group C guidelines are not part of a clinical trial, safety and effectiveness data are collected. Because administration of Group C drugs is not done with research intent, FDA has generally waived from the IRB review requirements [21 CFR 56.105]. Even though FDA has granted a waiver from these drugs, an IRB may still choose to conduct a review under its policies and procedures. The usage of a Group C drug is described in its accompanying “Guideline Protocol” document. The Guideline Protocol contains an FDA-approved informed consent document which must be used if there has been no local IRB review.

5.5 Parallel Track Studies

The FDA provides another mechanism for making promising investigational drugs and biologics available as quickly as possible for persons with AIDS and other HIV-related diseases, while generating data on the safety and effectiveness of the drugs. Under Parallel Track provisions, individuals with AIDS and HIV-related diseases for whom standard therapy is unsuitable or no longer effective, and who are not able to participate in on-going controlled clinical trials, have access to promising investigational drugs. Recipients of new drugs under Parallel Track provisions are actually participating in the studies although
without concurrent control groups. This mechanism is therefore called “Parallel Track Studies.”

Parallel Track protocols are considered a subset of the treatment IND are processed according to the treatment IND procedures described above. They are distinguished from other INDS merely by the amount of evidence of effectiveness required for FDA approval. Both are designated to make promising new agents available to persons with life-threatening diseases who cannot participate in controlled clinical trials and for whom there are no satisfactory alternative therapies. But while treatment INDs permit access to drugs in late Phase 2 and early Phase 3 stages of clinical trials, Parallel Track provisions permit access to AIDS drugs during late Phase 1 and early Phase 2 stages of clinical investigation. All Parallel Track requests must be reviewed by the IRB and the FDA.

In addition, Parallel Track studies are required to comply with the regulations governing informed consent, IRB review, and reporting requirements. Although the FDA may waive local IRB review for Parallel Track studies, the GHS Policy does not permit such waivers and requires IRB review and approval before any patients are treated under Parallel Track provisions. When submitting an application to use an investigational drug or biologic in a treatment protocol, the investigator should:

Identify the drug or biologic and provide the IND number under which it is currently being studied elsewhere (or under which it has been studied, if Phase 3 studies have been completed).

Explain the scientific basis for believing that the product may be useful for treating the patient’s condition and that it will not be unduly harmful.

Describe the patient population that would qualify for treatment with the product under the following criteria:

a. The patients are suffering from a serious or immediately life-threatening or severely debilitating disease, and
b. There is no comparable or satisfactory alternative drug or therapy available to treat the state of the disease in the intended population.

Submit a treatment protocol describing how the drug would be administered to qualified patients (including dosage, frequency, and mode of administration) and data that will be collected regarding their response to treatment.

Attach the consent form to be used. The only exception to the requirement for informed consent is if the drug must be administered in the emergency room or under similar emergency conditions.

Adverse event reports must be submitted as usual to the FDA and the IRB, and a report on the outcome of each patient treated must be provided to the IRB at intervals established by the IRB in compliance with the regulations of the FDA, as well as to the drug sponsor and the FDA as they may require.

6.0 STORAGE, DISPENSING AND CONTROL OF INVESTIGATIONAL DRUGS
Investigational drugs shall be stored in and dispensed from the hospital pharmacy for all inpatient research studies. Those studies being conducted in an outpatient setting shall make proper arrangements for dispensing investigational drugs.

Investigational drugs are the property of the sponsor, and any unused supplies shall be returned to the sponsor through the investigator upon completion of the study or upon the sponsor’s request.

Records of the receipt, distribution, and the return of investigational drugs shall be maintained by the pharmacy or the investigator if the study is conducted as an outpatient study.

7.0 INVESTIGATIONAL DEVICES

In accordance with GHS Policies and Procedures, investigational devices must be examined/approved by Biomedical Engineering prior to initiating use.

Investigational devices are to be utilized only by the individuals that have been approved by the IRB for said use. Any utilization by another individual will be considered research misconduct.

Should an emergency situation occur, the patient must be transferred to an approved investigator for device placement. For the patient’s safety, only those individuals trained in the use of the investigational device will be allowed access to the device.

8.0 HUMANITARIAN DEVICE EXEMPTIONS (HDE) AND HUMANITARIAN USE DEVICE (HUD)

Regulatory Background

The purpose of the HDE law and its implementing regulations 21 CFR 814 Subpart H is, to the extent consistent with the protection of the public health and safety and with ethical standards, to encourage the discovery and use of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States per year. 21 U.S.C 360j(m)(1) The law prescribes a method that permits a manufacturer to lawfully market a device without meeting the efficacy standards generally required for FDA pre-market approval of devices. After a manufacturer applies for an HDE, meets the regulatory requirements, and obtains FDA approval of HUD status, the HUD may be used in humans. However, the law permits the use of HUD’s only in facilities that have a local IRB and provided that the IRB approves the HUD’s use in the facility.

1 (A) the device is designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States per year. (B) the device would not be available to a person with a disease or condition referred to in subparagraph (a) unless the Secretary grants such an exemption and there is no comparable device, other than under this exemption, available to treat or diagnose such disease or condition, and (C) the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

U.S.C. 360j(m)(2)

8.1 IRB Responsibilities
The GHS IRB performs initial and continuing review of each HUD. For initial approval of a HUD, full board review is required; however, continuing review may take place under an expedited process. The physician utilizing the product pursuant to a HUD must report all SAE(s) and AE(s) to the GHS OHRP in accordance with these Policies & Procedures.

**Humanitarian Device Exemption (HDE) Regulation, Questions and Answers; Final Guidance for Industry** (July 12, 2001), Food and Drug Administration Center for Devices and Radiological Health. The FDA does not interpret the HDE law to require IRB review and approval for each individual use of the HUD. Thus it states that the law permits "the IRB to approve the use of the device in general, use of the device for groups of patients meeting certain criteria, or use of the device under a treatment protocol." [61 Fed. Reg 33232, 33235 (June 26, 1991)] In addition, if it desires, "an IRB may specify limitations on the use of the device based upon one or more measures of disease progression, prior use and failure of any alternative treatment modalities, reporting requirements to the IRB or IRB chairperson, appropriate follow-up precautions and evaluations, or any other criteria it determines to be appropriate."

8.2 **Informed Consent**

Since the HDE law does not require informed consent and because the FDA has determined that the humanitarian device exemption provides for temporary marketing approval, HUD use does not constitute "research" or an "investigation" which would normally require informed consent [61 Fed. Reg. 33232, 33235 (June 26, 1991)]. However, the FDA does not intend for the HUD waiver from 21 CFR Part 56 informed consent requirements to preempt institutional policies that require informed consent.

GHS OHRP policy requires written informed consent for the procedure in question unless immediate care is necessary to prevent jeopardy to the patient's life, limb, or mental wellbeing. Importantly, it should be noted that if the manufacturer wants to collect safety and effectiveness data in support of a pre-market approval (PMA) application, the informed consent requirements under Part 56 would apply.

8.3 **Application of 21 CFR 56.111 Approval Criteria**

The GHS IRB may minimize or ignore certain approval criteria when evaluating a HUD at the discretion of the Committee(s) and the Chairperson(s). Although the requirements of 21 CFR Part 56, including continuing review, "an IRB evaluating a HUD retains the discretion to minimize or ignore approval criteria that may be inappropriate in the treatment context (e.g., 'the importance of the knowledge that may be expected to result')." 61 Fed. Reg 33232, 33240

9.0 **OFF-LABEL DRUG RESEARCH**

Studies that use an approved drug for an unapproved indication that request a waiver of the IND must meet all of the following criteria of 21 CFR 312.2:

- The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- The investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR 56 and with the requirements for informed consent sent forth in 21 CFR 50 Subpart B; and
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7
- The drug product is lawfully marketed in the United States.

10.0 OFF-LABEL USE OF A HUD

In an emergency, a HUD may be used off-label, but FDA has stated that the emergency use rules for non-approved devices shall apply to HUDs. Namely, the physician should (if possible) seek prior concurrence of the IRB chairperson, informed consent, and an independent assessment from an uninvolved physician. Prior notice to the HDE holder is required. After the use, the physician must report to the HDE holder and to the IRB if not done previously. [for more information see *Humanitarian Device Exemption (HDE) Regulation, Questions and Answers; Final Guidance for Industry (July 12, 2001)*, Food and Drug Administration, Center for Devices and Radiological Health].

11.0 USER FACILITY ADVERSE EVENT REPORTING REQUIREMENTS

GHS IRB has to report to either or both the FDA and the manufacturer:

Death Reported Directly to FDA: "Whenever a user facility receives or otherwise becomes aware of information, from any source, that reasonably suggests that a device has or may have caused or contributed to the death of a patient of the facility, the facility shall as soon as practicable, but not later than 10 work days after becoming aware of the information" it must report to the FDA and to the manufacturer. *21 CFR 803.30(a)(1)*

Serious Injury Reported to Manufacturer: "Reports of serious injury. Whenever a user facility receives or otherwise becomes aware of information, from any source, that reasonably suggests that a device has or may have caused or contributed to a serious injury to a patient of the facility, the facility shall, as soon as practicable but not later than 10 work days after becoming aware of the information" report to the manufacturer. *21 CFR 803.30(a)(2)* If the manufacturer is unknown, the report shall be made directly to FDA.
1.0 DEFINITION

*Emergency Research*: A planned clinical investigation that is subject to FDA authorization in advance and involves subject(s) who are experiencing immediately life-threatening conditions for which available treatments are unproven or unsatisfactory.

2.0 EMERGENCY RESEARCH CONSENT EXEMPTION

The IRB may consider an "Emergency Research Consent Waiver" for a class of research consisting of activities, each of which have met the following strictly limited conditions under 21 CFR 50.24. For additional information on emergency research, refer to the document *Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research*.

**Research subject to FDA regulations**

The IRB responsible for the review, approval, and continuing review of the research activity has approved both the activity and a waiver of informed consent by documenting:

1. that the research activity *is subject* to the Food and Drug Administration (FDA) regulations (see Federal Register, Vol. 61, pp. 51498-51531) at 21 CFR Part 50 and will be carried out under an FDA investigational new drug application (IND) or an FDA investigational device exemption (IDE), the application for which has clearly identified the protocols that would include subjects who are unable to consent, and

2. that the requirements for exception from informed consent for emergency research detailed in 21 CFR 50.24 have been met relative to those protocols.

3. Documentation of the above criteria will be presented to the IRB by the PI completing the Planned Emergency Research Form (Appendix D) and reviewed by the IRB at a convened meeting as a full board review.

**Research not Subject to FDA regulations**

The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds, documents and reports to DHHS that each of the following conditions have been met relative to the research under 21 CFR 50.24:
1. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

2. Obtaining informed consent is not feasible because:

   (i) The subjects will not be able to give their informed consent as a result of their medical condition;

   (ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

   (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

3. Participation in the research holds out the prospect of direct benefit to the subjects because:

   (i) Subjects are facing a life-threatening situation that necessitates intervention;

   (ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

   (iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

4. The clinical investigation could not practicably be carried out without the waiver.

5. The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

6. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 21 CFR 50.25 and in accordance with 45 CFR 46.116 and 46.117. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible.

   (i) The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (7)(v) of this section.
7. Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible. For the purposes of this waiver “family member” means any one of the following legally competent persons: spouses; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the participant is the equivalent of a family relationship.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for
at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 21 CFR 56.115(b).

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 21 CFR 312.30 or 21 CFR 812.35.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.
Emergency use is defined as the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval for the use. 21 CFR 56.102 (d).

A test article is defined as a drug or device that is being tested for safety and effectiveness, not yet approved by the FDA for general use, or not yet approved for the particular use being researched. 21 CFR 56.102 (1).

The emergency use of a test article, other than a medical device, is a clinical investigation, the patient is a subject, 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 subjects, nor permit the outcome of such care to be included in any report of a research activity subject to DHHS regulations.

Emergency use of an investigational drug, device or procedure will be allowed only if all of the following requirements are met (21 CFR 56.102(d) and 56.104(c)):

1. A life-threatening or severely debilitating situation arises and there is no standard acceptable treatment available.
2. The situation necessitates the use of the investigational article.
3. There is not sufficient time to obtain prior IRB approval.
4. The investigator must make a follow-up report on any emergency use to the IRB within 5 working days.

The investigator will provide the IRB with the IND number of the investigational drug used.

This policy permits only a single emergency use for the treatment of one patient by one physician. If it appears probable that similar emergencies will require subsequent use of the test article, then a protocol should be developed and reviewed by the IRB for future use of the test article.

It is the responsibility of the investigator to obtain the consent form and have it on the patient’s chart at the time the use of the product is to begin.
The investigator is required to obtain the consent of the subject or the subject’s legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following 21 CFR 50.23:

1. The subject is confronted by a life-threatening situation necessitating the use of the test article.
2. Consent form cannot be obtained because of an inability to communicate with or obtain legally effective consent from the subject.
3. Time is not sufficient to obtain consent from the subject’s legal representative.
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the life of the subject.

The above written certification will be submitted to the IRB within 5 working days after the use of the test article.

If, in the investigator’s opinion, immediate use of the test article is required to preserve the subject’s life, and if time is not sufficient to obtain an independent physician’s determination that the four conditions noted in Section D apply, the clinical investigator shall make those written determinations, and within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article.

There must be clear documentation in the patient’s record for the emergent need of the test article. This must include potential benefit versus risk versus alternative treatments and any experienced adverse effects.

3.0 EMERGENCY USE NOTIFICATION AND REPORTING

The emergency use of an investigational drug or biologic agent with a patient in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval may occur if it is in the medical judgment of a physician that it is in the subject’s best interest. Any subsequent use of this test article is subject to IRB review and approval.

The physician must notify the IRB Chairperson prior to this emergency use or within 5 working days, but this notification is not to be construed as IRB approval. The patient, or legally authorized representative in accordance with FDA regulations, must sign a consent form. It is the responsibility of the investigator to obtain the consent form and have it on the patient’s chart at the time the use of the product is to begin. This patient is not considered a research subject and data from this patient may not be included in any report of the research. The physician must submit a written report of this emergency to the IRB within 5 working days.

When investigators provide prior notification of their intent to use a test article in an emergency or their intent to invoke the exception to the requirement to obtain consent, the IRB chairperson or designee reviews the notification to determine whether the circumstances would follow FDA regulations. The IRB chairperson or designee will also review the five-day reports of the emergency use of a test article and the exception to the requirement to obtain consent to determine whether the circumstances met FDA regulations.

There must be clear documentation in the patient’s record for the emergent need of the test article. This must include potential benefit versus risks versus alternative treatments and any experienced adverse effects.
Medical Devices: The emergency use of a medical device may occur if the patient is in a life-threatening condition that needs immediate treatment; there is no generally acceptable alternative for treating the patient and there is reason to believe that the medical device will provide a benefit; and because of the immediate need to use the device, there is no time to obtain IRB approval. The physician must notify the IRB Chairperson and FDA’s Center for Devices and Radiological Health prior to use of the device. These notifications are not to be construed as IRB approval. The patient, or legally authorized representative in accordance with FDA regulations, must sign a consent form. It is the responsibility of the investigator to obtain the consent form and have it on the patient’s chart at the time the use of the product is to begin. This patient is not considered a research subject and data from this patient may not be included in any report of the research. The physician must submit a written report of this emergency use to the IRB within 5 working days. Any subsequent use of this device is subject to IRB review and approval. Failure to report to the IRB within 5 working days constitutes research misconduct.

4.0 EMERGENCY USE OF A HUD

In an emergency, a physician can use a HUD prior to IRB approval if he or she determines that GHS IRB approval "can not be obtained in time to prevent serious harm or death to a patient." 21 U.S.C. 360j(m)(4)(B) [http://www.fda.gov/cdrh/ode/idepolicy.html Chapter III

In such a circumstance, the physician shall, after the use of the device, notify the chairperson of the GHS IRB of such use. Such notification shall include;

- the identification of the patient involved
- the date on which the device was used,
- and the reason for the use

5.0 OFF-LABEL USE OF A HUD

In an emergency, a HUD may be used off-label, but FDA has stated that the emergency use rules for non-approved devices shall apply to HUDs. Namely, the physician should (if possible) seek prior concurrence of the IRB chairperson, informed consent, and an independent assessment from an uninvolved physician. Prior notice to the HDE holder is required. After the use, the physician must report to the HDE holder and to the IRB if not done previously. [for more information see Humanitarian Device Exemption (HDE) Regulation, Questions and Answers; Final Guidance for Industry (July 18, 2006) Food and Drug Administration, Center for Devices and Radiological Health]. [http://www.fda.gov/cdrh/ode/guidance/1381.pdf]
Several issues are raised when a subject who is participating in a research study at one institution is admitted to another facility. To help illustrate, the following will serve as the model for this institution sheet: Regional Medical Center (RMC) has developed a research protocol; the study has been reviewed and approved by the RMC Institutional Review Board (RMC-IRB); each subject receives a test drug for a 16 week period (4 weeks inpatient, 12 weeks outpatient); some research subjects will live in a distant town with a local health care facility, Memorial Hospital (MH). For these subjects, participation at RMC will involve considerable travel time and costs. While several examples can be imagined, the three scenarios below may help to illustrate key points.

1. The least complex (first) scenario is when a subject’s treatment/hospitalization is not related to the research. Procedures should be in place for rapidly identifying test drugs and devices (e.g. an emergency contact number and unblinding procedure). For this example, we will assume that hospitalization at MH is medically necessary and that the local physician has determined that it is appropriate to continue the subject (now patient) on the test drug. In this case, MH is providing incidental medical care and is not participating as a research site. Therefore, MH staff are not investigators and the MH-IRB does not need to review the protocol. The usual procedures for dealing with drugs prescribed out-of-facility would be followed (often, this is a pharmacy department policy). The investigator at RMC remains responsible for test drug administration and follow-up and therefore, should be aware of the hospitalization. The RMC investigator may need to report the event as an unexpected adverse incident, if it is possibly related to use of the test article. The RMC-IRB remains the IRB of record.

2. For the second scenario, the involvement of MH is reasonably foreseen and is an anticipated part of the study protocol (e.g., the need for inpatient care is anticipated for the condition under study, or the need for subjects to return home and receive medical follow-up). The RMC-IRB should be aware that other institutions and/or providers will be providing medical care/follow-up and should ensure the adequate reporting and safety systems are in place before approving the study. In this example, the protocol allows the test drug to be sent to the subjects’ regular health care providers. Even though the test article is being given at MH, only routine medical monitoring is conducted by the local provider with little or no reporting to the RMC investigator, who remains responsible for the test drug administration and collects research data when the subject returns to RMC. The involvement of MH is incidental to the study (i.e. research data are not collected) and thus, it is not participating as a research site.

In the first two scenarios, prior to continuing the investigational drug, the local physician should obtain from the clinical investigator the information necessary to safely continue the investigational drug. The information conveyed might include a description of treatment procedures, warnings of possible adverse reactions, emergency procedures, a copy of the signed informed consent document (which is a research summary as well as a document of consent).
3. For the third scenario, MH is designated as an extension of the research milieu. In this instance, the second institution (MH) is responsible for a portion of the research protocol. For this example, a physician at MH has been identified in the protocol as a sub-investigator for subjects residing in that local catchment area. As sub-investigator, this physician is responsible for conducting examinations of subjects to monitor status and measure effects of the test drug (data collection). These research data are systematically reported to the RMC investigator.

Because MH is conducting research, it is responsible for complying with the applicable research regulations. The MH-IRB may review, approve and be responsible for monitoring the portion of the research conducted at MH just as it would for any other research in the facility or, MH may agree to accept the RMC-IRB as the responsible IRB. If the RMC-IRB is to accept responsibility for other sites, it should consider the rationale for transferring or referring subjects to another institution; the circumstances under which responsibility will be shared; the instructions that will be given to the sub-investigators; the monitoring procedures that will be followed; and the informed consent process.

1.0 INFORMED-consent

Although not specifically discussed in the FDA regulations, requiring the subject to sign a second consent form for the secondary facility should be avoided when feasible. In the first and second scenarios, research is not being conducted at MH and therefore, no research consent is needed for the second facility (however, consent for medical treatment may be required). Since the medical need in the first scenario is unexpected, the informed consent document would not describe such involvement. In the second scenario, because MH involvement is planned, the informed consent document should describe the activities to be carried out at MH. When some of the research activities are carried out at a secondary location, the investigator and the IRB should consider whether any additional information, such as local emergency contact number, needs to be included in the informed consent document.

The third scenario is the most complex. Because MH is involved in research, the informed consent process should include a description of this activity. As appropriate, this could be included in the consent document presented to all subjects, or a separate informed consent document could be prepared for those subjects entering MH. If the RMC-IRB is accepting responsibility for other sites, it would review and approve the informed consent document(s). If MH does not agree to cooperative review, however, MH-IRB may accept the RMC informed consent document if it adequately describes the involvement of MH (i.e., not require a second document). MH-IRB may also decide to develop its own informed consent document. In this case it is important that the subject not receive conflicting information and the two IRBs should work to resolve such issues. If there are two consent documents, generally the RMC document would cover the overall study and the MH document would only detail the specific procedures involved while at that facility.
Legal obligations to protect human subjects apply not only to direct contact with a human subject, but also to items that are derived from a human subject including medical records and biological specimens. For the purposes of this SOP, biological specimens can be broadly defined as a sample that originated from an organ system of a human. For example, this may include tissue samples (even when embedded in paraffin blocks), DNA, cells from the circulation or bone marrow, plasma, sera, feces, nail clippings and tissues removed for clinical purposes or due to a health condition (i.e. bowel from a surgical resection, tissue from an aborted fetus, embryos from a fertility clinic).

Such specimens may be collected for clinical purposes and stored per regulatory requirements for pathology accreditation, as part of a specific research study and then stored for future use, or as a purposeful collection of biological samples for the future distribution to investigators such as a repository. In addition, the collection, storage and use of such specimens might also be for the purposes of genetics research. In all of these scenarios, identifiable health information may or may not be associated with the biological sample.

Research studies which propose the collection and storage of human specimens are increasingly being submitted to the GHS Institutional Review Board (IRB) as proposals for the use of such specimens. The process should be thought of as having two stages: 1) the collection and storage of the specimens for current and/or future research purposes and 2) the use of previously collected/stored specimens for research purposes. Each stage requires IRB review and approval. Repositories require additional considerations. Lastly, issues of de-identification, confidentiality protections, and appropriate consenting procedures with respect to these studies are not straightforward, in part because The Common Rule (i.e., 45 CFR 46) and HIPAA differ with respect to what subjects must be told about the future uses of their samples when they agree to participate in specimen collection, storage, and/or use studies. For example, although the Common Rule would allow broader future use of stored specimens, HIPAA requires that future use be more specific. This SOP will marry the two sets of regulations.

For repository studies that require informed consent, an authorization must also be signed by the participant. Similarly, studies that obtain a waiver of informed consent will usually require a waiver of authorization.

If the IRB requires informed consent and authorization, HIPAA requires that authorizations must be specific. As such, subjects must be provided with specific information regarding the future use of their specimens if their samples are identifiable and such information is typically shared via the informed consent statement for the research project. For studies, which involve de-identified specimens, this issue does not apply. De-identified specimens may be used for broader purposes with appropriate IRB approval. For example, in a cancer study, subjects might be told in the informed consent that their specimens will be used “in relation to future research about cancer” and this would be HIPAA-compliant.

1.0 OBJECTIVES
The objectives of this SOP are to describe the appropriate ways to collect, store and use biological samples for research purposes.

2.0 SCOPE

This SOP applies to all personnel involved in the implementation and coordination of investigations involving human subjects by all departments of GHS. Personnel responsible: Principal Investigator/Co-investigator(s) and, when delegated by the investigator, sub-investigator(s), research coordinators, laboratory personnel handling biological samples, and other appropriately experienced and trained designated site personnel.

3.0 EXISTING COLLECTIONS OF HUMAN BIOLOGIC MATERIAL

Existing collections of human biologic material may have been developed over a period of time without use of written consent from subjects, or a limited consent from subjects may have been obtained during clinical procedures. Re-contact of donors may be difficult or impossible. In such situations, investigators should submit an application to the IRB for continued use (or a new use) of the collection or may adopt a policy to de-identify their collection. Such procedures to de-identify, per HIPAA standards, a collection should be approved by the IRB.

4.0 LEVEL OF IRB REVIEW

IRB approval is required under two scenarios for using biological specimens: retrospective use of previously stored specimens and prospective studies requesting the collection, storage or use of specimens for current and/or future research. Similarly, there are two categories of specimens: those obtained initially for clinical or diagnostic purposes only, and those obtained for research purposes.

NOTE: In all cases, a protocol describing the proposed research use of the specimens must be submitted to and approved by the IRB before the specimens are used.

The following information provides guidelines to help investigators better identify the appropriate process and level of review needed for a particular protocol. (NOTE: Also refer to Tables 1, 2, and 3).

Retrospective studies of already stored specimens, whether collected for clinical or research purposes, must obtain IRB approval. The level of review and issues of informed consent depends on the following:

- If samples are to be used in a de-identified manner, per HIPAA standards, (without linkage to subject identifiers), an investigator may request an exemption from full board review of a research protocol (see Table 1).

- If samples can be linked to identifiers either by the principal investigator or a third party, then such protocols will require either expedited or full board review (see Table 1). Depending on the nature of the protocol, the investigator may be required to obtain informed consent from the patients for the new use; however, waiver of consent may, at times, be appropriate.

- If prospectively collected specimens are to be used for research purposes the protocol must have IRB approval before they are collected and used. Some studies may qualify for expedited review but most will require full board review (see Table 2). If the investigator plans to store specimens from this protocol for future research use, the use must be specified and justified and be included in the consent form. If a future use is conceived that is different from the original
plan and from what was explained in the informed consent for which the subjects signed, then the specimens’ use in future protocols must be approved by the IRB by a new protocol or an amendment before the specimens are used. Depending on the study, the IRB may require the investigator to re-contact and/or re-consent all of the subjects before their specimens can be used in this or any subsequent study.

- **If prospectively collected specimens obtained for clinical or diagnostic purposes are to be used for research purposes**, then the specimens’ use in future protocols must be approved by the IRB before the specimens are used. Biological waste and left over specimens are included in this category. None of these studies will qualify for Exempt status, but will require either expedited or full board review. Depending on the nature of the protocol and whether or not identifiers are present, the investigator may be required to obtain informed consent from the patients for the new use either at the time their specimens are collected or retrospectively after their specimens were collected, but before the specimens may be used. This will be decided on a case-by-case basis (see Table 3).

- For research involving specimens from deceased individuals, HIPAA allows that such specimens may be used for any purpose as long as the investigator can attest that they are able to document that, if the specimen is identifiable, the individual is deceased. An exempt research application, however, will need to be submitted for IRB acceptance in order to proceed with the use.

**Retrospective Studies:**

**Table 1**

Research on Stored Human Biological Specimens (specimens already exist; have been collected and stored at the time of the IRB approval).

<table>
<thead>
<tr>
<th>Subject Identity</th>
<th>Genetic</th>
<th>Nongenetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anonymous</td>
<td>IRB Review</td>
<td>Consent</td>
</tr>
<tr>
<td>Identifiers known to third party</td>
<td>Full/Expedited</td>
<td>Maybe*</td>
</tr>
<tr>
<td>Identifiers known to P.I.</td>
<td>Full</td>
<td>Yes*</td>
</tr>
</tbody>
</table>

*Protocol for future use of banked specimen must be submitted to IRB. Consent may or may not be required by IRB for banking and/or use. If consent required, future use must be specific.

**Prospective Studies:**

**Table 2**

Biological Specimens obtained prospectively and procedures performed exclusively for current and future research

Prospective studies do not qualify for Exempt Review Procedures.

<table>
<thead>
<tr>
<th>Genetic</th>
<th>Nongenetic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subject Identity</strong></td>
<td>IRB Review</td>
</tr>
<tr>
<td>Anonymous or known</td>
<td>Full</td>
</tr>
</tbody>
</table>

Table 3

Biological Specimens obtained for clinical purposes to be used subsequently for current research or banking for future research (includes biologic waste and left over specimens).

<table>
<thead>
<tr>
<th>Genetic</th>
<th>Nongenetic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subject Identity</strong></td>
<td>IRB Review</td>
</tr>
<tr>
<td>Anonymous</td>
<td>Expedited</td>
</tr>
<tr>
<td>Identifiers known to third party only</td>
<td>Full</td>
</tr>
<tr>
<td>Identifiers known to P.I.</td>
<td>Full</td>
</tr>
</tbody>
</table>

*Consent may or may not be required by IRB. Consent for banking specimen must be obtained since specimens will be obtained prospectively. Protocol for specific future use of banked specimen must be submitted to the IRB.

5.0 **CREATION OF A REPOSITORY FOR FUTURE USE**

The concept of the creation of a biological specimen repository may include two kinds of samples: a) those collected with the expressed purpose of distribution to investigators, and b) those collected by individual investigators, and not originally intended to be shared with others, but which are subsequently shared as part of a repository. Any collection which contains specimens that are potentially identifiable and are distributed to someone other than the investigator (or, in the case of a multi-investigator study, other than any of the identified investigators) making the collection, regardless of the original intent, may be considered to be a repository. If housed at GHS, the repository must establish an oversight mechanism (such as a committee) to evaluate requests for samples for consistency with the IRB’s conditions for sharing samples and with the original informed consent.

5.1 **Features of a Formalized Repository**

Repository PI (“collector”) obtains IRB approval for establishing and maintaining the repository. The protocol clearly outlines the conditions under which the investigators share
specimens or data from the repository with Recipient Investigators (those who will receive specimens or data from the repository).

A “Submittal Agreement” is developed as part of the protocol that describes conditions for placing specimens in the repository. (see below)

**Submittal Agreement:** A written submittal agreement between the collector-investigators and recipient-investigators must require written informed consent of the donor-subjects utilizing an informed consent document approved by the local IRB where the collection will take place. It must also contain an acknowledgment that collector-investigators are prohibited from providing recipient-investigators with access to the identities of donor-subjects or to information through which the identities of donor-subjects may readily be ascertained. (See sample)

A “**Usage Agreement**” is developed as part of the protocol that describes those conditions for sharing specimens or data with Recipient Investigators. Both the Repository PI (or designee) and Recipient Investigator must sign the agreement.

**Usage Agreement:** A written usage agreement between recipient-investigators and collector-investigators must include the following: "Recipient acknowledges that the conditions for use of this research material are governed by the repository Institutional Review Board (IRB) in accordance with Department of Health and Human Services regulations at 45 CFR 46. Recipient agrees to comply fully with all such conditions and to report promptly to the repository any proposed changes in the research project and any unanticipated problems involving risks to subjects or others. Recipient remains subject to the recipient’s applicable State or local laws or regulations and institutional policies which provide additional protections for human subjects. This research material may only be utilized in accordance with the conditions stipulated by the repository IRB. Any additional use of this material requires prior review and approval by the repository IRB and, where appropriate, by an IRB at the recipient site, which must be convened under an applicable OHRP-approved Assurance.”

Repository PI is responsible for maintaining a copy of the signed Agreements and original informed consents.

The protocol must contain plans for protecting identifiers related to the specimen, and links between the identifiers and samples. OHRP strongly recommends that such condition stipulate that recipient-investigators not be provided access to the identities or donor-subjects or to information through which the identities of donor-subjects may readily be ascertained with the exception of data detailed in the informed consent. As such, GHS and their affiliates have adopted this requirement.

Each new use of a specimen must have IRB approval, and the Repository Investigator is responsible for ensuring that appropriate approval has been obtained and must allow for (1) the ability of someone (the GHS repository PI or the IRB) to identify donor-subjects; and (2) access of recipient investigators to donor-subject specific, but anonymous, protected health information in order to make research clinical relevant.

Use of samples from a repository must be restricted to the stipulations indicated in the original consent form used to procure the specimen, unless the sample is studied in a de-identified manner, in which case the sample may be used for unspecified purposes, or the
GHS IRB waives the requirement for consent and authorization. When identifiable samples are to be used, the recipient-investigator should submit to the IRB a copy of the consent that was originally used to collect the sample. As such, copies of this informed consent should be given to all recipient-investigators.

Investigators and repositories should maintain records to assure compliance with any specified restrictions of sample use that were explained in the protocol and informed consent the subject signed. GHS investigators receiving samples with identifiers or codes are legally and ethically responsible for maintaining the confidentiality of the subjects.

A Research Certificate of Confidentiality may need to be obtained from the federal government to protect confidentiality of repository specimens and data. The IRB will decide if this is necessary on a case-by-case basis. If the certificate of confidentiality is determined to be necessary, a copy must be submitted to the IRB that has oversight of the repository once received.

5.2 Consent Issues

The consent process and documentation (form), if required, must be approved by the GHS IRB. Elements of the consent process may be waived or modified by the GHS IRB. In general, prospective collection of coded or identified samples must be done using written consent. In minimal risk situations, identified or linked samples may qualify for consideration of waiver of consent or waiver of written documentation of (verbal) consent and waiver of authorization.

When informed consent to the research use of human specimens is required, it should be obtained separately from informed consent to clinical procedures (i.e., not combined with a general surgery or pathology consent). The person who obtains informed consent in the clinical setting should make clear to potential subjects that their refusal to consent to the research use of biological materials will in no way affect the quality of their clinical care.

In cases of biomedical research, GHS is obviously bound by the HIPAA regulations and since these regulations are stricter than what is prescribed by The Common Rule for such studies, GHS IRBs must adhere to the stricter requirements. Thus, the GHS IRBs require that for studies which involve the storage of identifiable samples, subjects must either be given specific information about what their samples might be used for in the future or they must be provided a subsequent informed consent (or the investigator must present the IRB with a justification for waiver of informed consent and receive approval for such a waiver from the IRB) when new uses are proposed with their samples that have not been previously described to them in an informed consent statement for which they signed. Future research is not always easy to define. For example, a specific use may be considered to be “studies related to cardiovascular disease,” “cancer,” “bone studies,” etc. The more sensitive the data to be released, the more specificity the IRB will require. For example, “future genetic research” would not be acceptable. If specimens will be stored in a de-identified manner, the future use does not have to be specifically described in the consent.

The informed consent statement must include the usual required elements of an informed consent (see OHRP Policy No.13.0). In addition, the use of biological samples requires special consideration of and explanation of the following issues:
Procedures for oversight of security and maintenance of the sample
- Who has access to the samples?
- Will the specimens be discarded if the PI leaves, or given to someone in the same Department?
- Will third parties, not part of the collection protocol, have use in the future? Is so, under what conditions?

Procedures to protect privacy and confidentiality of the information linked to the specimen and results obtained from analysis of the specimen.
- Will the specimen be de-identified per HIPAA standards?
- Will the specimen be linked to other information- if so who controls that link?
- Will results of analyses be linked back to the subject?
- How will the subject be able to revoke use of the specimens? [Note: In some cases, HIPAA allows that it may be acceptable to use the data already collected up to the point of revocation if elimination of the data could cause harm to the study results.]

Planned use of the specimen and potential future uses.
- According to the HIPAA, if the specimens are identifiable, the consent must clearly state the specific (or therapeutic area) use. If the specimens are de-identified, the consent may state that specimens may be used for unspecified research.
- Given the circumstances of the study, subjects should be offered right to consent for only specific use versus unspecified research.
- Repositories should clearly delineate the protocol and oversight.

Subjects’ rights and options for obtaining information of results obtained from use of the specimens:
- Will the subject not be given any information or will the subject have the option of learning of the results? If the latter is a possibility, how will this occur?
- Are there specific risks related to the type of tests/analyses (i.e. risk of insurance problems, embarrassment, social risk, or knowledge of the presence of a genetic mutation)?

Possible future contact, if any.
- Is it possible that the subject will be contacted for future information about themselves, or future use of the specimen? If so, the subject should be given the option of being contacted or not.
- For genetic studies, if the research investigator wishes to contact relatives of a proband, the proband must agree to this contact. If the proband declines to allow contact of relatives, the project may not proceed. If permission is granted for contact, the investigator must design a consent form to address the issue of information that may be forthcoming from the research project. The relatives should be given the option to decide whether they are willing to contribute samples. If they are willing to donate, they must be given the option of accepting or declining information derived from the research study.

Explanation that participant samples will be stored for future research purposes.
- Proposed use of stored samples [Note that per HIPAA regulations, future, unspecific use cannot be approved if samples will be stored in an identifiable manner].
- Procedures to protect the confidentiality and privacy of any personal identifiers that will be associated with the source of a specimen.

- Information about the control and management of the specimens during storage.
- The subject’s rights to withdraw his/her consent at any time either by requesting that the specimens be destroyed or that all personal identifiers be removed.

- Information about the length of storage.

- Whether the subject can obtain future access to the stored samples for information that may be of clinical relevance to him/her. Similarly, subjects must be told if such information will not be available in the future (e.g. because personal identifiers are to be removed).

- How the investigator will handle future third-party access.

- Information about possible secondary uses of the stored specimens, or the possible creation of an immortalized cell line based on the specimen, if applicable.

- Procedures for collecting and identifying specimens submitted to the repository.

- Who, in general, can use the repository?

- If and how the subjects are identified in the repository.

- Users of specimens from the repository will not know the identity of subjects.

- Whether or not subjects will be told the results of any screening done on specimens.

- Whether or not the subjects will derive any personal benefit.

- Physical risk of sample acquisition, if any.

- Potential fiscal, psychological, and social risks of disclosure of test results if results will be shared.

- Risks of participating in genetic studies including the effects of the knowledge that one is the carrier of a disease gene that might affect their life course, employability or insurability, if results will be shared. If subjects want to be told, precautions must be taken to minimize the potential harm of receiving bad news and to preserve the confidentiality of the results. The precautions needed in conveying genetic screening results depend upon the age of onset of the disorder, the burden of illness, and the availability of treatment or prevention. The communication of genetic information carries with it the responsibility to interpret the results and provide care for the
individual; and thus, it is ideally done in the setting of a clinical rather than research relationship with the subject.

- Risks to individual dignity, invasion of privacy, violation of confidentiality, stigmatization of a subject or group, discrimination in insurance or employment, psychological harm, generation of conflict within a family, harm to relatives, inappropriate commercialization of findings, or use of samples in projects objectionable to the subject.

- Describe procedures to minimize risks to subjects.

- Specify the general process for coding, identifying or anonymizing material.

- Indicate any security measures to be used to assure the continued anonymity of the donor.

- Indicate which individuals will have access to identifiers.

- If identified material is to be de-identified for use, indicate what consideration has been given to the fact that de-identification may deny the donor or the donor's descendants of assured or implied access to results of research.

- Indicate if access to existing medical records or contacting subjects is required for the project.

- Indicate under what circumstances it is anticipated that subjects may be contacted.

- If a certificate of confidentiality has been obtained, participants should be told and an explanation of what such a certificate means should be offered.

Examples: Depending on the nature of the research, subjects may be offered options such as:
- Permitting only unidentified or unlinked use of their biological samples in research,
- Permitting coded or identified use of their biological samples for one particular study only, with no further contact permitted to ask for permission to do further studies,
- Permitting coded or identified use of their biological samples for one particular study only, with further contact permitted to ask for permission to do further studies,
- Permitting coded or identified use of their biological samples for any study relating to the condition for which the sample was originally collected, with no further contact allowed to seek permission for other types of studies,
- Permitting coded or identified use of their biological sample for any study related to the condition for which the sample was collected with further contact allowed to seek permission for other types of studies.

If samples will be collected and subsequently sent to a repository or placed in a GHS repository, but the main aim of the study is the performance of a clinical trial, a separate consent form or a separate area within the main consent form which allows for a separate consent process must be provided for the sample collection and storage.
5.3 Other Less Common Considerations for the Consent

There may be situations where a patient or research subject is known to possess biologic specimens with unique characteristics thought to have commercial value. In this case, if specimens are to be collected for research purposes and the investigator expects that they will be commercialized into a marketable product or sent to a commercial sponsor for development, the consent form must state this possibility. IRB policy requires that the consent form contain the following language:

“As this is a research institution, specimens obtained in medical situations may later be used for research purposes. The investigator intends to include specimens taken from you along with other specimens that may also be used in an attempt to develop products to be sold, and it is not the intention of the investigator to enter into an agreement with you to become partners in sharing the profits or losses in the sale of those products.”

6.0 INFORMATION REQUIRED IN THE REPOSITORY PROTOCOL

In addition to all of the elements listed in the above informed consent section, the following should be included in the protocol submitted to the IRB for review:

1. Indicate the general nature of tests that will be done on the samples.
2. A full description of the mechanisms used to link specimens and identifiable information, and procedures used to maximize the protection against inadvertent release of confidential information.
3. If housed at GHS, the repository must establish a mechanism such as a committee to evaluate each request for samples by investigators to see if the request is consistent with the IRB’s conditions for sharing samples and with the original informed consent. The committee membership, and process, if applicable, should be outlined in the protocol submitted for IRB review.
4. If additional research is subsequently proposed that is not described in the current protocol, a new IRB application (or an amendment, if appropriate) must be submitted for review and approval.

7.0 APPLICABLE REGULATIONS AND GUIDELINES

45CFR46 Protection of Human Subjects (Common Rule)
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm
November 7, 1997 OPRR Guidance
(http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm)
HIPAA Privacy Rule:
HIPAA Privacy and Research Guidance:
http://privacyruleandresearch.nih.gov/

8.0 RESOURCES AND REFERENCES

Certificates of Confidentiality:
NHLBI Guidelines for Human Tissue Repository
http://www.nhlbi.nih.gov/funding/policies/repos-gl.htm
The IRB is responsible for ensuring the equitable selection of research subjects. 21 CFR 56.111(a)(3) In fulfilling this responsibility, the IRB must review:

- The information contained in the advertisement(s);
- The mode of their communication;
- The final copy of the printed advertisement(s);
- The final audio/video taped advertisement(s).

The advertising must be reviewed by the IRB to ensure that advertisement(s):

- Do not state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol;
- Do not include exculpatory language;
- Do not emphasize the payment or the amount to be paid, by such means as larger or bold type;
- Do not promise “free treatment” when the intent is only to say participants would not be charged for taking part in the investigation.

Any advertisement(s) to recruit subjects should be limited to:

- The name and address of the clinical investigator.
- Purpose of the research and, in summary form, the eligibility criteria that will be used to admit subjects into the study.
- A straightforward and truthful description of the benefits (e.g., payments or free treatments) to the subject for participation in the study.
- A statement describing what aspect of the research is investigational.
- A statement that risks involved in the research will be discussed with interested persons.
- The location of the research and the person to contact for further information.
- The time or other commitment required of the participant(s).

For FDA-regulated research:

- Do not use terms, such as “new treatment”, “new medication” or “new drug” without explaining that the test article is investigational;
- Do not include compensation for participation in a trial offered by a sponsor to involve a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

No claim should be made, either explicitly or implicitly, that the drug, device or procedure is safe or effective for the purpose under investigation that are consistent with FDA labeling, or that the drug, device or procedure is in any way equivalent or superior to any other drug or device or procedure.

Advertisements may be reviewed and approved by the Chairperson or Vice-Chairperson via expedited review process or through the convened IRB process.

The IRB will review payments to determine that:
The amount of payment and the proposed method and timing of disbursement is neither coercive nor presents undue influence;

Credit for payment accrued as the study progressed and is not contingent upon the participant completing the entire study;

Any amount paid as a bonus for completion is reasonable and not so large as to unduly induce participants to stay in the study when they would otherwise have withdrawn;

The IRB prohibits:

- Payments to professionals in exchange for referrals of prospective participants (“finder’s fees”);
- Payments designed to accelerate recruitment that are tied to the rate or timing of enrollment (“bonus payments”) unless they are judged not to interfere with providing prospective participants with sufficient opportunity to consider whether to participate and did not increase the possibility of coercion or undue influence on investigators or participants.
1.0 PURPOSE

To establish guidelines regarding industry sponsored research that is submitted for review to a GHS IRB.

2.0 IRB REMITTANCE

1. Any commercially funded study submitted to the IRB for review will be assessed a fee for IRB review. The check should be addressed to the Greenville Health System. The GHS Office of Human Research Protection will provide an invoice. The PI of research sponsored by GHS or a GHS affiliate may apply for a waiver of fees as determined by the GHS OHRP.

2. This fee is a minimal assessment to cover the administrative overhead cost of the IRB. This fee will cover initial and continuing review, a reasonable number of amendment/revision approvals, and review of adverse events for the life of this institution.

3. If amendments/revisions are so significant that the study must repeat initial review, the IRB may, at its discretion, charge an additional review fee.

4. Investigators are informed of this fee through the IRB’s Guidelines for Submitting Research.

3.0 CLINICAL TRIAL AGREEMENTS

1. The PI must ensure that the written contract with the industry sponsor or Contract Research Organization (CRO) will require that the PI follow ICH-GCP, applicable federal and state law, and the protocol. The research coordinator will review the contract to verify the contract contains these items.

2. The PI must ensure that a written contract with the industry sponsor address responsibility for providing medical care for research related injury including both clinical and financial responsibilities. The research coordinator will review the contract to verify the contract contains these items.

3. The PI must ensure that a written contract requiring the industry related sponsor to promptly report (within 30 days) report to the Greenville Health System’s OHRP/IRB any findings affecting participant safety or participants’ continued voluntary participation to be reported to the GHS IRB. The research coordinator will review the contract to verify the contract contains these
items.

4. The PI must ensure that a written contract with the industry related sponsor describes the steps followed to communicate findings from a closed research study to the researcher or Health System when those findings directly affect participant safety. The timeframe from communicating these findings must be no longer than within 2 years of the closure of the study. The research coordinator will review the contract to verify the contract contains these items.

5. The PI must ensure that a written contract with the industry related sponsor requires the sponsor to promptly (no longer than within 30 days) report to the Health System any findings that could influence the conduct of the study or alter the IRB’s approval to continue the study. The research coordinator will review the contract to verify the contract contains these items.

6. The PI must ensure that a written contract with the industry related sponsor specifies the timeframe for providing the Greenville Health System’s OHRP/IRB routine and urgent data and safety monitoring reports, as indicated in the IRB-approved data and safety monitoring plan approved by the IRB. The research coordinator will review the contract to verify the contract contains these items.

7. The PI must ensure that a written contract with industry-related sponsor includes the following:
   - will publish, and/or disclose to participants, important information discovered in the study that affects the interests of research participants and the medical care they receive;
   - requires the sponsor to have the primary responsibility for data and safety monitoring that includes a provision to advise the IRB of the monitoring plans and provide periodic reports to the IRB.

The research coordinator will review the contract to verify the contract contains these items.

8. The GHS Institutional Official is responsible for the review and endorsement of the contract on behalf of the GHS.

9. The PI and/or research coordinator will forward a copy of the finalized signed contract of each study to the GHS Contracts Coordinator for entry in the GHS contract repository.

4.0 Guidance for Additional Compliance Requirements for Federal Agencies Other Than OHRP or FDA Who May Sponsor, Fund, or Oversee Human Subjects Research

Most of the sponsored research conducted by GHS researchers is subject only to DHHS (OHRP) or FDA oversight and requirements given forth in 45 CFR 46 or 21 CFR 50, 56, 312 and 812. However, when research is sponsored by another federal department, agency or office, those entities may have additional human subjects protection requirements with which investigators are expected to comply.

The following is a listing of some of those additional requirements.

Department of Defense (DOD)

Researchers are responsible for communicating with their DoD Program Officer to ensure that all DoD requirements are met prior to starting an IRB approved study.
• Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research - DoD INSTRUCTION Number 3216.02 November 8, 2011

**Department of Energy (DOE)**

Researchers are responsible for communicating with their DoE Program Officer to ensure that all DoE requirements are met prior to starting an IRB approved study

- DOE Human Subjects Protection Program
- Human Subjects Regulations, Orders, and Policies
- Protection of Human Research Subjects - DOE ORDER O 443.1B Approved 3-17-2011

**Department of Education**

Researchers are responsible for communicating with their Department of Education Program Officer to ensure that all requirements of the Department of Education are met prior to starting an IRB approved study

- Family Educational Rights and Privacy Act (FERPA)
- Protection of Pupil Rights Amendment (PPRA) (20 U.S.C. § 1232h; 34 CFR Part 98)
- 34 CFR Part 98 - Student Rights in Research, Experimental Programs and Testing
- HIPA & FERPA - Joint guidance from Departments of Education and Health & Human Services

**Department of Justice (DoJ)**

**Bureau of Prisons (BOP)**

Researchers are responsible for communicating with the Bureau of Prisons (the Bureau) to ensure that all Bureau requirements are met prior to starting an IRB approved study.

- Code of Federal Regulations (CFR) Title 28 Judicial Administration Part 512 - Research
- BOP Program Statement on Research

**National Institute of Justice (NIJ)**

Researchers are responsible for communicating with their NIJ Program Officer to ensure that all NIJ requirements are met prior to starting an IRB approved study.

- Human Subjects and Privacy Protection
- For NIJ-funded research, data must be submitted to the National Archive of Criminal Justice Data (NACJD)

**Environmental Protection Agency (EPA)**

Researchers are responsible for communicating with their EPA Program Officer to ensure that all EPA requirements are met prior to starting an IRB approved study

- 40 CFR Part 26 - Protection of Human Subjects
International Conference on Harmonisation (ICH)

Researchers are responsible for complying with the International Council on Harmonisation (ICH) - Good Clinical Practice (GCP) Guidelines (E6) when required by the sponsor.

- Good Clinical Practice (GCP) Guidance (E6)

National Institutes of Health

- Belmont Report - Ethnical Principles and Guidelines for the protection of human subjects of research
- Stem Cell Information - Frequently Asked Questions (FAQs)

ClinicalTrials.gov

ClinicalTrials.gov is a registry and results database of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov gives you information about a trial's purpose, who may participate, locations, and phone numbers for more details. This information should be used in conjunction with advice from health care professionals.

General Requirements

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;

Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

"Applicable clinical trials" generally include interventional studies (with one or more arms) of drugs, biological products, or devices that are subject to FDA regulation, meaning that the trial has one or more sites in the U.S, involves a drug, biologic, or device that is manufactured in the US (or its territories), or is conducted under an investigational new drug application (IND) or investigational device exemption (IDE). For the complete statutory definitions and more detailed information on the agency's current thinking about their meaning, see this pdf document.

HIPAA - Health Insurance Portability and Accountability Act

The Office for Civil Rights enforces the HIPAA Privacy Rule, which protects the privacy of individually identifiable health information; the HIPAA Security Rule, which sets national standards for the security of electronic protected health information; and the confidentiality provisions of the Patient Safety Rule, which protect identifiable information being used to analyze patient safety events and improve patient safety.
1.0 INITIAL EDUCATION REQUIREMENTS

All researchers (principal investigators, co-investigators, other research staff, and students) involved in human subject research must complete training prior to submitting a study protocol for IRB review. Investigators must undertake the requisite education via the CITI Training Course. Investigators are required to review the institutional instructions and select the appropriate education modules on the CITI web page.

Effective January 1, 2008, individuals without CITI training certification are not allowed to participate in a research project conducted at the Greenville Health System or under its aegis. The Greenville Health System authorizes OHRP leadership (OHRP Director, OHRP Medical Director, Chief Science Officer/Institutional Official) to suspend research participation of any investigator deemed noncompliant with the training mandate outlined above. OHRP leadership may also suspend or terminate any study including investigators noncompliant with training mandates.

2.0 CONTINUING RESEARCH EDUCATION REQUIREMENTS

All researchers (principal investigators, co-investigators, and research staff) actively involved in human subject research must complete continuing education training every three (3) years. This requirement must be accomplished via CITI Training at the same website CITI Training Course. Researchers will be automatically notified by CITI Program registration when the Refresher Course is due.

IRB Coordinators will verify whether CITI education requirements are current, including bi-annual re-qualification for all studies submitted for initial approval.

Researchers who do not intend to engage in further research may decline completing continuing education. However, should that researcher later decide to conduct a study, he/she and staff are required to complete the entire research education program.
### 1.0 TRAINING FOR IRB MEMBERS

GHS and ORHP provides/facilitates training for IRB members and their alternates, including the following:

- Policies and Procedures Manual for the IRB;
- Website for the GHS Office of Human Research Protection as well as the eIRB Portal Home for electronic submissions;
- The Belmont Report;
- 45 CFR 46;
- 21 CFR 50 and 56;
- Reviewer checklists for New Studies/Continuing Review and Amendments to be used as tools and thinking points when performing a review;
- Tutorial on How do I perform a Review as a Designated Reviewer?;
- Tutorial on How do I perform a Review as a Non-Designated Reviewer?;

### 2.0 INITIAL EDUCATION REQUIREMENTS

All IRB members are required to complete the IRB Member modules via the CITI Training Course. Monthly ongoing education sessions are also presented at each IRB meeting.

### 3.0 CONTINUING EDUCATION REQUIREMENTS

All IRB members must complete continuing education training every three (3) years. This requirement must be accomplished via CITI Training at the same website CITI Training Course. Researchers will be automatically notified by CITI Program registration when the Refresher Course is due.
All Preparatory to Research requests must be submitted to the GHS IRB using the GHS Request to Access Protected Health Information Preparatory to Research Form, available from the GHS OHRP website http://hsc.ghs.org/eirb/forms or the IRB office.

An investigator may request access to protected health information maintained by GHS to determine if sufficient data exists to prepare a research protocol related to a specific disease(s).

HIPAA regulations require the investigator agree to the following:

Use or disclosure of protected health information is sought solely to determine if sufficient data exists to prepare a research protocol.

No protected health information will be removed from GHS premises in the course of the review.

The protected health information for which use or access is sought is necessary for the research purposes.

The requestor must be a member of the GHS medical staff or a GHS employee who is a licensed clinical staff professional. Research education must be completed before the request will be processed.

If access is requested by someone other than the investigator, the investigator must define the role of the designee as related to the research.

For purposes of this request, “protected health information” means any information, including demographic information, created or received by GHS and healthcare providers furnishing services at any GHS site that (1) is related to the past, present or future physical or mental health of an individual, the provision of health care to an individual, or the past, present or future payment for the provision of health care to an individual; and (2) identifies the individual or it is reasonable to believe the information can be used to identify the individual.

The PI is required to submit this form to an OHRP/IRB Coordinator for processing. The Coordinator will forward the submission to the OHRP Medical Director (alternatively, IRB Committee Chair or Vice Chair) for approval. Upon approval, the PI, and his/her designee identified in this request, may access protected health information maintained by GHS to inform subsequent development of a study protocol.
1.0 SCOPE

The Privacy Rule regulates health care groups, organizations, or businesses, called covered entities under the Rule, handle the individually identifiable health information known as protected health information (PHI). Researchers should comply with the Privacy Rule because it establishes the conditions under which covered entities may use or disclose PHI for many purposes, including for research. While the Privacy Rule may not apply to all researchers, the manner in which the Rule protects PHI could affect certain aspects of research.

2.0 DEFINITIONS

**Health Insurance Portability and Accountability Act of 1996 (HIPAA)** – contains provisions to protect the confidentiality and security of personally-identifiable information that arises in the course of providing health care. To clarify HIPAA’s impact on research, note the legal definitions below.

**Authorization** – under HIPAA, the granting of rights to access PHI. Authorization is required by HIPAA for disclosures or uses other than for Treatment Procedures Operations (TPO), which are covered in the Notice of Privacy Practices. Treatment cannot be conditioned on granting of an authorization. An authorization is a specific, detailed document requesting patient-subject permission for the use of covered PHI.

**Covered Entities** – a health plan, a health care clearinghouse, or a health care provider who transmits health information in electronic form in connection with a transaction for which HHS has adopted a standard.

**Disclosure** – the release, transfer, provision of access to, or divulging in any other manner of information outside the entity holding the information.

**Health Care Provider** – a provider of services (as defined in section 1861(u) of the Act, 4 U.S.C. 1395x(u)), a provider of medical or health services (as defined in section 1861(s) of the Act 42, U.S.C. 1395x(s)), and any other person or organization who furnishes, bills, or is paid for health care in the normal course of business.

**Health Information** – any information, whether oral or recorded in any form or medium, that (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.
**Individually Identifiable Health Information** – information that is a subset of health information, including demographic information collected from an individual, and (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual; and (a) that identifies the individual; or (b) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

**Minimum Necessary Standard** – the least information reasonably necessary to accomplish the intended purpose of the use, disclosure, or request of PHI.

**Notice of Privacy Practice** – The HIPAA Privacy Rule gives individuals a fundamental right to be informed of the privacy practices of their health plans and of most of their health care providers, as well as to be informed of their privacy rights with respect to their personal health information. Health plans and covered health care providers are required to develop and distribute a notice that provides clear explanations of these rights and practices. The Notice of Privacy Practices is intended to focus on individual privacy issues and concerns, and to prompt them to have discussions with their health plans and health care providers and exercise their rights. Note: Sometimes the Notice of Privacy Practice is interchangeable with PHI.

**Protected Health Information (PHI)** – PHI is individually identifiable health information transmitted by electronic media, maintained in electronic media, or transmitted or maintained in any other form or medium. PHI excludes education records covered by the Family Educational Rights and Privacy Act, as amended, 20 U.S.C. 1232g, records described at 20 U.S.C. 1232g(a)(4)(B)(iv), and employment records held by a covered entity in its role as employer.

**Research** – a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. This includes the development of research repositories and databases for research.

**Research Health Information (RHI)** – is defined as data used in research that would be personally identifiable but not considered PHI and is therefore not subject to the HIPAA Privacy and security Rules. The key distinction between RHI and PHI is that PHI is associated with or derived from a healthcare service event, i.e. the provision of care or payment for care. RHI is covered by the other state and federal laws for privacy and confidentiality of research health information.

### 3.0 COVERED ENTITIES

HIPAA defines covered entities as (1) health plans, (2) health care clearinghouses, and (3) health care providers who electronically transmit any health information in connection with transactions for which HHS has adopted standards. Generally, these transactions concern billing and payment for services or insurance coverage. For example, hospitals, academic medical centers, physicians, and other health care providers who electronically transmit claims transactions information directly or through an intermediary to a health plan are covered entities. Covered entities can be institutions, organizations, or persons.

Researchers are covered entities if they are also health care providers who electronically transmit health information in connection with any transaction for which HHS has adopted a standard. For example, physicians who conduct clinical studies or administer experimental therapeutics to
participants during the course of a study must comply with the Privacy Rule if they meet the HIPAA definition of a covered entity.

4.0 BUSINESS ASSOCIATES

The Privacy Rule also protects individually identifiable health information when it is created or maintained by a person or entity conducting certain functions on behalf of a covered entity – a business associate. A business associate is a person or entity, who is not a member of the workforce and performs or assists in performing, for or on behalf of a covered entity, a function or activity regulated by the HIPAA Administrative Simplification Rules, including the Privacy Rule, involving the use or disclosure of individually identifiable health information, or that provides certain services to a covered entity that involve the use or disclosure of individually identifiable health information. Because HIPAA Administrative Simplification Rules do not directly regulate research activities, the Privacy Rule does not require a researcher or a research sponsor to become a business associate of a covered entity for research purposes. However, a covered entity may engage business associates to assist in the de-identifying PHI, to prepare limited data sets, or to perform data aggregation. The Privacy Rule requires a covered entity to enter into a written contract, or another arrangement permitted by the Rule if both parties are government entities, with its own business associates. The Rule’s business associate provision can be found in Section 164.502(e) and 164.504(e). Generally, a covered entity may, for the purposes permitted by the Privacy Rule and specified in its written agreement with its business associate, disclose PHI to that business associate and allow the business associate to use, create, or receive PHI on its behalf. Before the covered entity discloses the PHI to the business associate, the covered entity must obtain satisfactory assurances, generally in the exceptions, the contract may not authorize the business associate to use or further disclose the PHI in a manner that would violate the Privacy Rule if done directly by the covered entity.

5.0 RESEARCH AND HIPAA

The HIPAA Privacy Rule primarily addresses information generated in the course of health care service provision. However, HIPAA does recognize that some research may create, use, and disclose Protected Health Information (PHI).

HIPAA defines research using the federal Common Rule (45 CFR 46), which is a systematic investigation designed to contribute to generalizable knowledge.

In practice, investigators may assume they are conducting research if they intend to publish the study results. Quality improvement project solely intended to improve clinical practice is not categorized as research if the analyses and results are restricted to internal use. However, researchers should anticipate whether future publication is possible, because the IRB will not grant research approval with person-identifiable records retroactively.

6.0 WHAT INFORMATION IS PROTECTED BY THE PRIVACY RULE?

The Privacy Rule defines PHI as individually identifiable information, held or maintained by a covered entity or its business associates acting for the covered entity that is transmitted or maintained in any form or medium (including the individually identifiable health information of non-U.S. citizens). This includes identifiable demographic and other information relating to the past, present, or future physical or mental health or condition of an individual, or the provision or payment of health care to an individual that is created or received by a health care provider, health plan, employer, or health care clearinghouse. For purposes of the Privacy Rule, genetic information is considered to be health information.
The Privacy Rule applies only to individually identifiable health information held or maintained by a covered entity or its business associate acting for the covered entity. Individually identifiable health information that is held by anyone other than a covered entity, including an independent researcher who is not a covered entity, is not protected by the Privacy Rule and may be used or disclosed without regard to the Privacy Rule. There may, however, be other Federal or State protections covering the information held by these entities that limit its use or disclosure.

7.0 RESEARCH THAT IS COVERED BY HIPAA

HIPAA affects only that research which creates, or discloses Protected Health Information (PHI). In general, there are two ways a research study would involve PHI.

- The study involves review of medical records as one (or the only) source of research information. Prospective studies may do this also, such as when a researcher contacts a participant’s physician to obtain or verify some aspect of a person’s health history.
- The study creates new medical records because as part of the research of a health-care service is being performed, such as testing of new way of diagnosing a health condition or a new drug or device for treating a health condition.

Most sponsored clinical trials that submit data to the US Food and Drug Administration (FDA) will involve PHI because study monitors have an obligation to compare research records such as Case Report Forms (CRFs) to the medical records of the persons participating in the study, in order to verify that the information transcribed onto the CRFs is accurate.

8.0 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for identifying in his/her application to the IRB all proposed access to PHI which will occur during the course of the research, including access to paper and electronic medical records for the purpose of subject identification or screening, any intended addition of information into medical records, and any collection or use of human specimens with individually identifiable health information attached.

The investigator is responsible for identifying and complying with HIPAA policies and procedures, as well as applicable State or Federal regulations governing access to PHI outside the GHS covered entity.

9.0 HOW CAN COVERED ENTITIES USE AND DISCLOSE PROTECTED HEALTH INFORMATION FOR RESEARCH AND COMPLY WITH THE PRIVACY RULE?

The Privacy Rule describes the ways in which covered entities can use or disclose PHI, including for research purposes. In general, the Rule allows covered entities to use and disclose PHI for research if authorized to do so by the subject in accordance with the Privacy Rule. In addition, in certain circumstances, the Rule permits covered entities to use and disclose PHI without Authorization for certain types of research activities. For example, PHI can be used or disclosed for research if a covered entity obtains documentation that an Institutional Review Board (IRB) or Privacy Board has waived the requirement for Authorization or allowed an alteration. The Rule also allows a covered entity to enter into a data use agreement for sharing a limited data set. There are also separate provisions for how PHI can be used or disclosed for activities preparatory to research and for research on decedents’ information.
In order to comply with the HIPAA accounting requirement, research personnel must implement GHS Privacy Policy P-9, and/or for outside investigators your own privacy policy, which would require research investigators to maintain a confidential database of the names of all patients or research study participants whose PHI was used or disclosed or activities preparatory to research or under an IRB Waiver of Authorization.

It is important to note that there are circumstances in which health information maintained by a covered entity is not protected by the Privacy Rule. PHI excludes health information that is de-identified according to specific standards. Health information that is de-identified can be used and disclosed by a covered entity, including a researcher who is a covered entity, without Authorization or any other permission specified in the Privacy Rule. Under the Privacy Rule, covered entities may determine that health information is not individually identifiable in either of two ways.

### 9.0.1 De-identifying Protected Health Information Under the Privacy Rule

Covered entities may use or disclose health information that is de-identified without restriction under the Privacy Rule. Covered entities seeking to release this health information must determine that the information has been de-identified using either statistical verification of de-identification or by removing certain pieces of information from each record as specified in the Rule.

The Privacy Rule allows a covered entity to de-identify data by removing all 18 elements that could be used to identify the individual or the individual’s relatives, employers, or household members; these elements are enumerated in the Privacy Rule. The covered entity also must have no actual knowledge that the remaining information could be used alone or in combination with other information to identify the individual who is the subject of the information. Under this method, the identifiers that must be removed are the following:

<table>
<thead>
<tr>
<th>1. Names</th>
<th>5. Facsimile numbers.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of Census:</td>
<td>6. Electronic email addresses.</td>
</tr>
<tr>
<td>a. The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people.</td>
<td>7. Social security numbers.</td>
</tr>
<tr>
<td>b. The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.</td>
<td>8. Medical record numbers.</td>
</tr>
<tr>
<td>3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.</td>
<td>9. Health plan beneficiary numbers.</td>
</tr>
<tr>
<td>4. Telephone numbers.</td>
<td>10. Account numbers.</td>
</tr>
<tr>
<td></td>
<td>12. Vehicle identifiers and serial numbers, including license plate numbers.</td>
</tr>
<tr>
<td></td>
<td>14. Web universal resources locators (URLs).</td>
</tr>
<tr>
<td></td>
<td>15. Internet protocol (IP) address numbers.</td>
</tr>
<tr>
<td></td>
<td>16. Biometric identifiers, including fingerprints and voiceprints.</td>
</tr>
<tr>
<td></td>
<td>17. Full-face photographic images and any comparable images.</td>
</tr>
<tr>
<td></td>
<td>18. Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.</td>
</tr>
</tbody>
</table>
Covered entities may also use statistical methods to establish de-identification instead of removing all 18 identifiers. The covered entity may obtain certification by “a person with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable” that there is a “very small” risk that the information could be used by the recipient to identify the individual who is the subject of the information, alone or in combination with other reasonably available information. The person certifying statistical de-identification must document the methods used as well as the result of the analysis that justifies the determination. A covered entity is required to keep such certification, in written or electronic format, for at least 6 years from the date of its creation or the date when it was last in effect, whichever is later.

9.0.2 Other Issues Relating to De-identification

Under the first method, unique identifying numbers, characteristics, or codes must be removed if the health information is to be considered de-identified. However, the Privacy Rule permits a covered entity to assign to, and retain with, the health information a code or other means of record identification if that code is not derived from or related to the information about the individual and could not be translated to identify the individual. The covered entity may not use or disclose the code or other means of record identification for any other purpose and may not disclose its method of re-identifying the information. For example, a randomly assigned code that permits re-identification through a secured key to that code would not make the information to which it is assigned PHI, because a random code would not be derived from or related to information about the individual and because the key to that code is secure.

A covered entity is permitted to de-identify PHI or engage a business associate to de-identify PHI. For example, a researcher may be a covered entity him/herself performing, or may be hired as a business associate to perform, the de-identification. In most cases, the covered entity must have a written contract with the business associate containing the provisions required by the Privacy Rule before it provides PHI to the business associate. In addition, a covered entity, if a hybrid entity, could designate in its health care component(s) portions of the entity that conduct business associate-like functions, such as de-identification.

De-identifying PHI according to Privacy Rule standards may enable many research activities; however, the Privacy Rule recognizes that researchers may need access to and generate identifiable health information during the course of research. Where PHI is needed for research activities, the Privacy Rule permits its use and disclosure if certain standards are met. These standards are discussed in the following sections.

10.0 AUTHORIZATION FOR RESEARCH USE AND DISCLOSURES

One way the Privacy Rule protects the privacy of PHI is by generally giving individuals the opportunity to agree to the uses and disclosures of their PHI by signing an Authorization form for uses and disclosures not otherwise permitted by the Rule. The Privacy Rule establishes the right of an individual, such as a research subject, to authorize a covered entity to use and disclose his/her PHI for research purposes. This requirement is in addition to the informed consent to participate in research required under the HHS Protection of Human Subjects Regulations and other applicable Federal and State law.
10.0.1 Elements of an Authorization

A valid Privacy Rule Authorization is an individual’s signed permission that allows a covered entity to use or disclose the individual’s PHI for the purposes, and to the recipient or recipients, as stated in the Authorization. When an Authorization is obtained for research purposes, the Privacy Rule requires that it pertain only to a specific research study, not to nonspecific research or to future, unspecified projects. The Privacy Rule considers the creation and maintenance of a research repository or database as a specific research activity, but the subsequent use or disclosure by a covered entity of information from the database for a specific research study will require separate Authorization unless the PHI use or disclosure is permitted without Authorization (discussed later in this section). If an Authorization for research is obtained, the actual uses and disclosures made must be consistent with what is stated in the Authorization. The signed Authorization must be retained by the covered entity for 6 years from the date of creation or the date it was last in effect, whichever is later. An Authorization differs from an informed consent in that an Authorization focuses on privacy risks and states how, why, and to whom the PHI will be used and/or disclosed for research. An informed consent, on the other hand, provides research subjects with a description of the study and of its anticipated risks and/or benefits, and a description of how the confidentiality of records will be protected, among other things. An Authorization can be combined with an informed consent document or other permission to participate in research. Whether combined with an informed consent or separate, an Authorization must contain the following specific core elements and required statements stipulated in the Rule:

10.0.2 Authorization Core Elements

- A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner.
- The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure.
• The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure.

• A description of each purpose of the requested use or disclosure.

• Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure (“end of the research study” or “none” are permissible for research, including for the creation and maintenance of a research database or repository).

• Signature of the individual and date. If the individual’s legally authorized representative signs the Authorization, a description of the representative’s authority to act for the individual must also be provided.

10.0.3 Authorization Required Statements

• A statement of the individual’s right to revoke his/her Authorization and how to do so, and, if applicable, the exceptions to the right to revoke his/her Authorization or reference to the corresponding section of the covered entity’s notice of privacy practices.

• Whether treatment, payment, enrollment, or eligibility of benefits can be conditioned on Authorization, including research-related treatment and consequences of refusing to sign the Authorization, if applicable.

• A statement of the potential risk that PHI will be re-disclosed by the recipient. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.

The Privacy Rule does not specify who may draft the Authorization, so a researcher could draft it regardless of whether the researcher is a covered entity. However, in order to have a Privacy Rule-compliant Authorization, it must be written in plain language and contain the core elements and required statements, and a signed copy must be provided to the individual signing it if the covered entity itself is seeking the Authorization.

NOTE: If an Authorization permits disclosure of the individual’s PHI to a person or organization that is not a covered entity or a business associate acting on behalf of a covered entity (such as a sponsor or funding source of the research), the Privacy Rule does not continue to protect the PHI disclosed to such entity. However, other applicable Federal and State laws between the disclosing covered entity and the PHI recipient may establish continuing protections for the disclosed information. Under the HHS Protection of Human Subjects Regulations or the FDA Protection of Human Subjects Regulations, an IRB may impose further restrictions on the use or disclosure of research information to protect subjects.

An Authorization for research uses and disclosures need not have a fixed expiration date or state a specific expiration event; the form can list “none” or “the end of the research project.” However, although an Authorization for research uses and disclosure need not expire, a research subject has the right to revoke, in writing, his/her Authorization at any time. The individual’s revocation is effective, except to the extent that the covered entity has taken action in reliance upon the Authorization prior to revocation. For example, a covered entity is not required to retrieve information that it disclosed under a valid Authorization before learning of the revocation. And the preamble to the Privacy Rule states that, for research uses and disclosures, the reliance exception would permit the continued use and disclosure of PHI already obtained with an Authorization to the extent necessary to protect the integrity of the research—for example, to account for a subject’s withdrawal from the research study, to conduct investigations of scientific misconduct, or to report adverse events.

11.0 WAIVER OR ALTERATION OF THE AUTHORIZATION REQUIREMENT
Many health research projects and protocols cannot be undertaken using health information that has been de-identified. Also, it may not be feasible for a researcher to obtain a signed Authorization for all PHI the researcher needs to obtain for the research study. In other cases, a researcher may determine that consents obtained prior to April 14, 2003, that permit the use and disclosure of information obtained from research subjects are inadequate, insufficient, or restrict the research protocol or procedure such that an Authorization may be necessary to permit the PHI use or disclosure for the research.

To address these and other situations that may arise in the course of a research project or protocol, the Privacy Rule contains criteria for waiver or alterations of Authorizations by an IRB or another review body called a Privacy Board. Many of the provisions were modeled on the HHS Protection of Human Subjects Regulations. The Privacy Rule does not change current requirements that specify when researchers must submit protocols to the IRB for review and approval, and obtain informed consent documents. The Privacy Rule adds to such requirements only when a researcher requests a waiver or an alteration of Authorization. If a covered entity has used or disclosed PHI for research with an IRB or Privacy Board approval of waiver or alteration of Authorization, documentation of that approval must be retained by the covered entity for 6 years from the date of its creation or the date it was last in effect, whichever is later.

For research uses and disclosures of PHI, an IRB or Privacy Board may approve a waiver or an alteration of the Authorization requirement in whole or in part. A complete waiver occurs when the IRB or Privacy Board determines that no Authorization will be required for a covered entity to use and disclose PHI for a particular research project. A partial waiver of Authorization occurs when an IRB or Privacy Board determines that a covered entity does not need Authorization for all PHI uses and disclosures for research purposes, such as disclosing PHI for research recruitment purposes. An IRB or Privacy Board may also approve a request that removes some PHI, but not all, or alters the requirements for an Authorization (an alteration).

The Privacy Rule does not alter IRB membership requirements, jurisdiction on matters concerning the protection of human subjects, or other procedural IRB matters. The Privacy Rule states that the required documentation must indicate that the IRB followed normal or expedited procedures in reviewing and approving the waiver or alteration. Thus, an IRB’s authority to act on waiver or alteration requests under the Privacy Rule is in addition to the other authorities derived from the HHS Protection of Human Subjects Regulations and other applicable statutes and regulations. The process and criteria for obtaining a waiver of Authorization under the Privacy Rule is similar to the process and criteria for waiving informed consent in the HHS Protection of Human Subjects Regulations. Additional information on the Privacy Rule and IRBs can be found in the companion piece entitled Institutional Review Boards and the HIPAA Privacy Rule.

Privacy Boards are new, alternative review boards authorized by the Privacy Rule to review requests for alteration or waiver of a research Authorization. If a covered entity is to use or disclose PHI on the basis of a waiver or an alteration of Authorization from a Privacy Board, the Board must be established in accordance with Section 164.512 of the Privacy Rule. These provisions state that:

- Members must have varying backgrounds and appropriate professional competencies as necessary to review the effect of the research protocol on individuals’ privacy rights and related interests.
- Each Board must have at least one member who is not affiliated with the covered entity or with any entity conducting or sponsoring the research and who is not related to any person who is affiliated with such entities.
- Members may not have conflicts of interest regarding the projects they review.

Additional information on the Privacy Rule and Privacy Boards can be found in the companion piece entitled *Privacy Boards and the HIPAA Privacy Rule.*

Documentation of the waiver or alteration of Authorization must include a statement identifying the IRB or Privacy Board that made the approval and the date of approval. Among other things, the documentation must also include statements that the IRB or Privacy Board has determined that the waiver or alteration of Authorization, in whole or in part, satisfies the following criteria:

1. The use or disclosure of the PHI involves no more than minimal risk to the privacy of individuals based on, at least, the presence of the following elements:
   a. An adequate plan to protect health information identifiers from improper use and disclosure.
   b. An adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so).
   c. Adequate written assurances that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

2. The research could not practicably be conducted without the waiver or alteration.

3. The research could not practicably be conducted without access to and use of the PHI.

The Privacy Rule does not require an IRB or Privacy Board to review the form or content of the Authorization a researcher or covered entity intends to use, or the proposed uses and disclosures of PHI made according to an Authorization. Under the Privacy Rule, an IRB or Privacy Board need only review requests to waive or alter the Authorization requirement.

Many research projects take place at multiple sites and/or require the use and disclosure of PHI created or maintained by more than one covered entity (collectively, *multisite projects*). Often, different IRBs are involved in multisite project reviews. The same situation is expected to occur with Privacy Boards. In some circumstances, Privacy Boards and IRBs will coexist. Where these boards coexist, the Privacy Rule does *not* require approval of a waiver or an alteration of Authorization by both bodies because a covered entity may rely on a waiver or an alteration of Authorization approved by any IRB or Privacy Board, without regard to the location of the approver.

HHS has stated (*65 Federal Register* 82692, December 28, 2000) that a covered entity’s responsibility is to “obtain the documentation that one [emphasis added] IRB or privacy board has approved the alteration or waiver of Authorization.” Consequently, the Privacy Rule allows a waiver or an alteration of Authorization obtained from a single IRB or Privacy Board to be used to obtain PHI in connection with a multisite project. However, HHS also recognizes that “covered entities may elect to require duplicate IRB or Privacy Board reviews before disclosing [PHI] to requesting researchers” (*67 Federal Register* 53232, August 14, 2002). While the Privacy Rule does not address potential splits between IRBs and Privacy Boards, HHS “strongly encourages researchers to notify IRBs and privacy boards of any prior IRB or privacy board review of a research protocol” (*65 Federal Register* 82692, December 28, 2000).
<table>
<thead>
<tr>
<th>Area of Distinction</th>
<th>HIPAA Privacy Rule</th>
<th>HHS Protection of Human Subjects Regulations Title 45 CFR Part 46</th>
<th>FDA Protection of Human Subjects Regulations Title 21 CFR Parts 50 and 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review of Cooperative Research</td>
<td>Requests to waive or alter the Authorization requirement are reviewed and approved by an IRB or Privacy Board. The Privacy Rule permits a covered entity to reasonably rely on the determination of an IRB or Privacy Board, if the covered entity obtains appropriate documentation of such determination.</td>
<td>Each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with the HHS Protection and Human Subjects Regulations. With the approval of HHS, an institution participating in a cooperative project may enter into a joint review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.</td>
<td>Cooperative research/multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoiding duplication of effort.</td>
</tr>
<tr>
<td>Waivers of Authorization Consent Requirements</td>
<td>Allows waiver or alteration of Authorization when IRB or Privacy Board deems the following criteria are met: (1) use or disclosure involves no more than minimal risk to the privacy of individuals because of the presence of at least the following elements: (a) An adequate plan to protect health information identifiers from improper use or disclosure, (b) an adequate plan to destroy identifiers at the earliest opportunity absent a health or research justification or legal requirement to retain them, and (c) adequate written assurances that the PHI will not be used or disclosed to a third party except as required by law, for authorized oversight of the research study, or for other research uses and disclosures permitted by the Privacy Rule; (2) research could not practicably be conducted without the waiver of alteration; and (3) research could not practicably be conducted without access to and use of PHI.</td>
<td>Permits an IRB to waive some or all of the elements of informed consent, or to waive the requirement to obtain informed consent, provided by the IRB finds and documents that (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.</td>
<td>Permits FDA to waive IRB Review requirements.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Permits an IRB to approve a clinical investigation without subjects’ informed consent in certain circumstances specified in 21 CFR 50.23 and 21 CFR 50.24. These include (1) circumstances in which immediate use of the test article is, in the investigator’s opinion, required to preserve the life of the subject; and time is not sufficient to obtain informed consent; (2) circumstances when the U.S. President may waive informed consent for military personnel for administration of an investigational product to members of the armed forces; and (3) circumstances involving emergency research.</td>
<td>Permits an IRB to approve a clinical investigation without subjects’ informed consent in certain circumstances specified in 21 CFR 50.23 and 21 CFR 50.24. These include (1) circumstances in which immediate use of the test article is, in the investigator’s opinion, required to preserve the life of the subject; and time is not sufficient to obtain informed consent; (2) circumstances when the U.S. President may waive informed consent for military personnel for administration of an investigational product to members of the armed forces; and (3) circumstances involving emergency research.</td>
</tr>
</tbody>
</table>
12.0 LIMITED DATA SET AND DATA USE AGREEMENT

The Privacy Rule permits a covered entity, without obtaining an Authorization or documentation of a waiver or an alteration of Authorization, to use and disclose PHI included in a limited data set. A covered entity may use and disclose a limited data set for research activities conducted by itself, another covered entity, or a researcher who is not a covered entity if the disclosing covered entity and the limited data set recipient enter into a data use agreement. Limited data sets may be used or disclosed only for purposes of research, public health, or health care operations. Because limited data sets may contain identifiable information, they are still PHI.

A limited data set is described as health information that excludes certain, listed direct identifiers (see below) but that may include city; state; ZIP Code; elements of date; and other numbers, characteristics, or codes not listed as direct identifiers. The direct identifiers listed in the Privacy Rule’s limited data set provisions apply both to information about the individual and to information about the individual’s relatives, employers, or household members. The following identifiers must be removed from health information if the data are to qualify as a limited data set:

1. Names.
2. Postal address information, other than town or city, state, and ZIP Code.
3. Telephone numbers.
4. Fax numbers.
5. Electronic mail addresses.
7. Medical record numbers.
8. Health plan beneficiary numbers.
11. Vehicle identifiers and serial numbers, including license plate numbers.
12. Device identifiers and serial numbers.
13. Web universal resource locators (URLs).
14. Internet protocol (IP) address numbers.
15. Biometric identifiers, including fingerprints and voiceprints.
16. Full-face photographic images and any comparable images.

A data use agreement is the means by which covered entities obtain satisfactory assurances that the recipient of the limited data set will use or disclose the PHI in the data set only for specified purposes. Even if the person requesting a limited data set from a covered entity is an employee or otherwise a member of the covered entity’s workforce, a written data use agreement meeting the Privacy Rule’s requirements must be in place between the covered entity and the limited data set recipient. The Privacy Rule requires a data use agreement to contain the following provisions:

• Specific permitted uses and disclosures of the limited data set by the recipient consistent with the purpose for which it was disclosed (a data use agreement cannot authorize the recipient to use or further disclose the information in a way that, if done by the covered entity, would violate the Privacy Rule).
• Identify who is permitted to use or receive the limited data set.
• Stipulations that the recipient will
  ▪ Not use or disclose the information other than permitted by the agreement or otherwise required by law.
  ▪ Use appropriate safeguards to prevent the use or disclosure of the information, except as provided for in the agreement, and require the recipient to report to the covered entity any uses or disclosures in violation of the agreement of which the recipient becomes aware.
• Hold any agent of the recipient (including subcontractors) to the standards, restrictions, and conditions stated in the data use agreement with respect to the information.
• Not identify the information or contact the individuals.
If a covered entity is the recipient of a limited data set and violates the data use agreement, it is deemed to have violated the Privacy Rule. If the covered entity providing the limited data set knows of a pattern of activity or practice by the recipient that constitutes a material breach or violation of the data use agreement, the covered entity must take reasonable steps to correct the inappropriate activity or practice. If the steps are not successful, the covered entity must discontinue disclosure of PHI to the recipient and notify HHS.

Section 164.512 of the Privacy Rule also establishes specific PHI uses and disclosures that a covered entity is permitted to make for research without an Authorization, a waiver or an alteration of Authorization, or a data use agreement. These limited activities are the use or disclosure of PHI preparatory to research and the use or disclosure of PHI pertaining to decedents for research.

13.0 RESEARCH ON DECEDETS’ PROTECTED HEALTH INFORMATION

Research on decedent (deceased persons) information is still protected under the HIPAA Privacy Rule even though it is not covered by the Common Rule regulations (45 CFR 46) and thus does not require IRB approval.

To use or disclose PHI of the deceased for research, covered entities are not required to obtain Authorizations from the personal representative or next of kin, a waiver or an alteration of the Authorization, or a data use agreement. However, the covered entity must obtain from the researcher who is seeking access to decedents’ PHI (1) oral or written representations that the use and disclosure is sought solely for research on the PHI of decedents, (2) oral or written representations that the PHI for which use or disclosure is sought is necessary for the research purposes, and (3) documentation, at the request of the covered entity, of the death of the individuals whose PHI is sought by the researchers.

14.0 OTHER USES AND DISCLOSURES OF PROTECTED HEALTH INFORMATION

Some of the PHI uses and disclosures that are permitted under the Privacy Rule at Section 164.512 without Authorization, waiver or alteration of Authorization, or data use agreement are summarized below. Covered entities seeking to use and disclose PHI for these or other purposes permitted under Section 164.512 should consult the Privacy Rule for information on the relevant implementation requirements.

Among other limited purposes, a covered entity may use or disclose PHI without an Authorization, as follows:

To the extent the use or disclosure is required by law and complies with, and is limited to, the relevant requirements of such law. For example, a covered entity may disclose, without Authorization, PHI to cancer registries if the disclosure (or reporting) is required by law. In addition, a covered entity may disclose to the Federal Government, without Authorization, PHI associated with data first produced under a Federal award in accordance with 45 CFR 74.36 http://www.access.gpo.gov/nara/cfr/waisidx_01/45cfr74_01.html

- For disclosure to a public health authority that is authorized by law to collect or receive the information for purposes of preventing or controlling disease, injury, or disability. Activities included here are reporting disease, injury, and vital events, such as birth or death, as well as conducting public health surveillance, investigations, and interventions. For example, a covered entity may disclose PHI, without Authorization, related to an adverse event to NIH or FDA as public health authorities. Additional guidance on the use and disclosure of PHI for

- To a person subject to the jurisdiction of the FDA with respect to an FDA-regulated product or activity for which that person has responsibility, for purposes related to the quality, safety, or effectiveness of the FDA-regulated product or activity (including, but not limited to, adverse event reporting; FDA-regulated product tracking; post-marketing surveillance; and enabling product recalls, repairs, replacements, or look back). For example, a covered entity may disclose adverse event/safety reports to sponsors of investigational new products.

- To health oversight agencies for oversight activities authorized by law that are necessary, for example, for the appropriate oversight of government-regulated programs. For example, because Office for Human Research Protections (OHRP) is a health oversight agency under the Privacy Rule, a covered entity may disclose PHI, without Authorization, to OHRP for purposes of determining compliance with the HHS Protection of Human Subjects Regulations.

15.0 MINIMUM NECESSARY RESTRICTION

With some exceptions, the Privacy Rule imposes a minimum necessary requirement on all permitted uses and disclosures of PHI by a covered entity. This means that a covered entity must apply policies and procedures, or criteria it has developed, to limit certain uses or disclosures of PHI, including those for research purposes, to “the information reasonably necessary to accomplish the purpose [of the sought or requested use or disclosure].” For uses and routine and recurring disclosures of and requests for PHI, the covered entity must develop policies and procedures (which may be standard protocols) to reasonably limit such uses, disclosures, and requests to the minimum necessary to achieve the purpose of the use or disclosure. For non-routine disclosures and requests, a covered entity must review each disclosure or request individually against criteria it has developed.

There are several exceptions to the minimum necessary requirements that may affect researchers (Sections 164.502(b) and 164.514(d) of the Privacy Rule). The minimum necessary standard does not apply to the following:

- Uses and disclosures made with an individual’s Authorization.
- Disclosures to, or requests by, a health care provider for treatment.
- Disclosures to the individual.
- Uses or disclosures required by law.
- Disclosures to HHS for purposes of determining compliance with the Privacy Rule.
- When required for compliance with other HIPAA rules (e.g., to fill out required or situationally required data fields in standard transactions).

Unless otherwise excepted, covered entities are required to implement policies and procedures or establish criteria that limit the PHI used, disclosed, or requested to the minimum amount reasonably necessary to achieve the purposes (e.g., necessary for the specific research) for which disclosure is sought. These covered entity policies and procedures will apply to researchers who are members of the covered entity’s workforce and may apply to business associates.

The Privacy Rule does not require a covered entity to independently determine, in all instances, whether a request for PHI meets the minimum necessary requirement. As relevant here, the Privacy Rule permits the covered entity to rely, when reasonable, on a request for disclosure of PHI as the minimum necessary when making permitted disclosures to public officials, disclosing information
requested by another covered entity, or when disclosing PHI to researchers who have documentation of an IRB or Privacy Board waiver or alteration of Authorization or certain other representations permitted by the Privacy Rule, which are discussed in detail in related publications, *Institutional Review Boards and the HIPAA Privacy Rule* and *Privacy Boards and the HIPAA Privacy Rule*.

The GHS IRB functions as the privacy board. They may grant waivers of the research authorization requirement described in this policy and per the Privacy Rule. The GHS Privacy Office will be consulted as needed.

The Office of Human Research Protection should be contacted at 455-8997 or the GHS Privacy Office at 797-7755 with any questions.

**16.0 HOW ARE SUBJECTS’ RIGHTS AFFECTED BY THE PRIVACY RULE?**

In addition to establishing conditions for the use and disclosure of PHI, the Privacy Rule establishes certain rights of individuals with respect to their health information. Covered entities must provide individuals with written notice of the entity’s privacy practices and the individual’s privacy rights. In addition, the Rule permits individuals to gain access to, request amendment of, request restrictions on, and request confidential communication of certain records related to their health care. Individuals are also given the right to request and receive a written account from a covered entity of when and why their PHI has been disclosed without their Authorization, except under limited circumstances. Individuals also have the right to complain to the covered entity and to the Secretary of Health and Human Services if they believe a violation of the Privacy Rule has occurred. This document discusses an individual’s rights to access PHI and receive an accounting of PHI disclosures.

**16.0.1 Access to Protected Health Information**

With few exceptions, the Privacy Rule guarantees individuals access to their medical records and other types of health information to the extent the information is maintained by the covered entity or its business associate within a designated record set. Research records maintained by a covered entity may be part of a designated record set if, for example, the records are medically related or are used to make decisions about research participants.

In most cases, patients or research subjects can have access to their health information in a designated record set at a convenient time and place. One exception, among others, is during a clinical trial, when the individual’s right of access can be suspended while the research is in progress if, in consenting to participate in research including treatment, the individual agreed to the temporary denial of access. The covered entity, however, must inform the individual that the right to access his/her health records in the designated record set will be restored upon conclusion of the clinical trial.

**16.0.2 Accounting for Disclosures of Protected Health Information**

The Privacy Rule permits individuals to obtain a record of certain disclosures of their PHI by covered entities or their business associates, including certain disclosures made by researchers who must comply with the Rule. This is known as an accounting of disclosures. It is important to emphasize the difference between a use and a disclosure of PHI. In general, the use of PHI means communicating that information within the covered entity. A disclosure of PHI means communicating that information to a person or entity outside the covered entity, or the communication of PHI from a health care component to a non-health care
component of a hybrid entity. The Privacy Rule restricts both uses and disclosures of PHI, but it requires an accounting only for certain PHI disclosures.

Upon receiving an individual’s request, a covered entity must account for disclosures of that individual’s PHI made on or after the covered entity’s compliance date (for most entities, April 14, 2003), unless a particular disclosure or type of disclosure is excluded from this accounting requirement in Section 164.528(a) of the Privacy Rule. For example, an accounting is not needed when the PHI disclosure is made:

- For treatment, payment, or health care operations.
- Under an Authorization for the disclosure.
- To an individual about himself or herself.
- As part of a limited data set under a data use agreement.
- Prior to the compliance date.

An individual’s right to receive an accounting of disclosures (unless an exception applies) starts with the covered entity’s compliance date and goes back 6 years from the date of the request, not including periods prior to the compliance date. A covered entity must therefore keep records of such PHI disclosures for 6 years.

The Privacy Rule allows three methods for accounting for research-related disclosures that are made without the individual’s Authorization or other than a limited data set: (1) A standard approach, (2) a multiple-disclosures approach, and (3) an alternative for disclosures involving 50 or more individuals. Whatever approach is selected, the accounting is made in writing and provided to the requesting individual. Accounting reports to individuals may include results from more than one accounting method.

**Standard Accounting**

Standard accounting includes, for each disclosure, the following information:

- The date the disclosure was made.
- The name and, if known, address of the person or entity receiving the PHI.
- A brief description of the PHI disclosed.
- A brief statement of the reason for the disclosure.

**Multiple Disclosures Accounting**

Multiple disclosures accounting is permissible if the covered entity has made multiple disclosures of PHI to the same person or entity for a single purpose under Sections 164.502(a)(2)(ii) or 164.512 of the Privacy Rule. For each disclosure, the following must be included:

- The date the initial disclosure was made during the accounting period.
- The name and, if known, address of the person or entity receiving the PHI.
- A brief description of the PHI disclosed.
- A brief statement of the reason for the disclosure.
- The frequency, periodicity, or number of the disclosures made during the accounting period.
- The date of the last such disclosure during the accounting period.
Alternative Accounting

If a covered entity has made disclosures regarding 50 or more individuals for a particular research project under Section 164.512(i) of the Privacy Rule, the accounting may be limited to the following information:

- The name of the protocol or research activity.
- A plain-language description of the research protocol or activity, purpose of the research, and criteria for selecting particular records.
- A description of the type of PHI disclosed.
- The date or period of time during which the disclosure(s) occurred or may have occurred, including the date of the last disclosure during the accounting period.
- The name, address, and telephone number of the entity that sponsored the research and of the researcher who received the PHI.
- A statement that the individual’s PHI may or may not have been disclosed for a particular protocol or research activity.

If the covered entity uses the alternative accounting method, it must, if requested to by the individual, assist the individual in contacting the research sponsor and the researcher. Such assistance, however, is limited to those situations in which there is a reasonable likelihood that the individual’s PHI was actually disclosed for the research protocol or activity.

17.0 GHS INFORMED CONSENT REQUIREMENTS REGARDING HIPAA

The GHS IRB provides an authorization template that complies with HIPAA requirements. The template language must be included in all informed consent forms that are submitted to the IRB for review:

18.0 CONTACT FOR QUESTIONS

The Office of Human Research Protection should be contacted at 455-8997 or the GHS Privacy Office at 797-7755 with any questions.

19.0 SOURCES OF INFORMATION ABOUT THE PRIVACY RULE

HIPAA Privacy Rule

- The final HIPAA Privacy Rule is available at http://www.hhs.gov/ocr/hipaa

Agencies

- Office for Civil Rights (OCR), Department of Health and Human Services (HHS) http://www.hhs.gov/ocr/hipaa
- Agency for Healthcare Research and Quality (AHRQ) http://www.ahrq.gov/
- Centers for Disease Control and Prevention (CDC) http://www.cdc.gov/mmwr/preview/mmwrhtml/m2e411a1.htm
- Food and Drug Administration (FDA) http://www.fda.gov/
• National Institutes of Health (NIH)  
  http://privacyruleandresearch.nih.gov/
• Office for Human Research Protections (OHRP), HHS  
  http://www.hhs.gov/ohrp
• Substance Abuse and Mental Health Services Administration (SAMHSA)  
  http://www.hipaa.samhsa.gov/
The Greenville Health System
Office of Human Research Protection
HRPP Policies and Procedures

Title: Research Repositories, Databases, and the HIPAA Privacy Rule

1.0 SCOPE

The Privacy Rule was not intended to impede research using records within databases and repositories that include individual’s health information but the Privacy Rule does place conditions on the use and disclosure of PHI by covered entities for research. The creation of a research database or repository, and the use or disclosure of PHI from a database or repository, is considered research under the Privacy Rule.

Thus, the creation of a database to be used for research purposes requires IRB approval.

2.0 USE OF GHS PROTECTED HEALTH INFORMATION (PHI) FOR ACTIVITIES PREPARATORY TO RESEARCH

All Preparatory to Research requests must be submitted to the GHS IRB using the GHS Preparatory to Research Form, which is available from the GHS OHRP website http://www.ghs.org/research or the IRB office.

An investigator may request access to protected health information maintained by GHS to determine if sufficient data exists to prepare a research protocol related to a specific disease(s).

HIPAA regulations require the investigator agree to the following:

Use or disclosure of protected health information is sought solely to determine if sufficient data exists to prepare a research protocol.

No protected health information will be removed from GHS premises in the course of the review.

The protected health information for which use or access is sought is necessary for the research purposes.

The requestor must be a member of the GHS medical staff or a GHS employee who is a licensed clinical staff professional. CITI training must be completed before the request will be processed.

If access is requested by someone other than the investigator, the investigator must define the role of the designee as related to the research.

For purposes of this request, “protected health information” means any information, including demographic information, created or received by GHS and healthcare providers furnishing services at any GHS site that (1) is related to the past, present or future physical or mental health of an
individual, the provision of health care to an individual, or the past, present or future payment for the provision of health care to an individual; and (2) identifies the individual or it is reasonable to believe the information can be used to identify the individual.

Once this request has been received and approved by the GHS Institutional Review Committee, the PI, and his/her designee that have been identified in this request, may access protected health information maintained by GHS for the purposes described in the request.

A copy of the approved Preparatory to Research form must be presented to Medical Information prior to any protected health information (PHI) being released.

According to HHS guidance on the Privacy rule,

The preparatory to research provision permits covered entities to use or disclose protected health information for purposes preparatory to research, such as to aid study recruitment. However, the provision at 45 CFR 164.512 does not permit the researcher to remove protected health information from the covered entity’s site. As such, a researcher who is an employee or a member of the covered entity’s workforce could use protected health information to contact prospective research subjects [emphasis added]. The preparatory research provision would allow such a researcher to identify prospective research participants for purposes of seeking their Authorization to use or disclose protected health information for a research study.
1.0 INTRODUCTION
The Research Compliance Auditor/Internal Reviewer evaluates research processes to ensure GHS’ human subjects research meets the highest quality standards, complies with all applicable federal and state regulations, and complies with GHS policies. Researchers should consider the auditor/internal reviewer a partner in regulatory compliance and agency inspection readiness.

2.0 OBJECTIVE
1. To describe the audit process, detailing what will be audited and when auditing will occur.
2. To describe the process for audit reports and identify report recipients.
3. To describe the process for when and how an audit response is required, completed and submitted.

3.0 SCOPE
These policies and procedures apply to all research activities of faculty, staff, student, or others who are involved in human subject research that fall under the jurisdiction of the GHS Institutional Review Board.

4.0 PURPOSE
Audits ensure study teams abide by proper scientific, ethical and regulatory requirements as outlined in Institutional Review Board approved clinical protocols. The program also encourages compliance by detecting errors and/or omissions occurring inadvertently in the course of research activities. This Program educates and enhances academic research practice.

Additionally, the Program provides faculty and staff information on regulatory compliance and Good Clinical Practice (GCP) Guidelines concerning human subjects, data collection and data management. The program also verifies protection of human subject’s rights and welfare, verifies investigator compliance with the currently approved IRB protocol, and applicable regulatory requirements; the program also verifies that reported study data are accurate, complete and verifiable from the source documents. Finally, the program investigates complaints and/or allegations of noncompliance with research regulations.

Goal
Maintain compliance with applicable rules in order to protect patient (research subject), Principal Investigator and their staff, and Greenville Health System.

Assumptions
The Audit process will be Cooperative, Collaborative and Educational rather than punitive.
Process
Selection of audits/internal review is done on a priority basis. Audits/Internal Review requested by the IRB will occur as first priority. Second priority: Research studies approved for new investigators and/or new sites with enrolled subjects will be chosen for audit within the first 8 months of approval. Third priority: Research studies that are due for re-approval will be chosen randomly each month.

Investigator directed “For Cause” audits/internal review will be in collaboration with the IRB in that it will be partly based on the risks and concerns associated with studies.

The Medical Director of the GHS OHRP may make changes to the auditors'/internal reviewer assignments as needed.

Provide a quarterly audit schedule that includes:
— no more than 2 recommended studies per each IRB Coordinator per month (random and non-random)
— directed audit(s) by IRB(s)
— previous audit follow-up
— Auditor discretionary choices (random and non-random)
— Medical Director and/or Administrator recommendations

Audit schedule affirmed by Medical Director.

Audit request is sent to affected Principal Investigators/Study Coordinators.

Following the on-site audit the auditor/internal reviewer will communicate the audit findings (informal common report from the research site and the IRB files) to the GHS OHRP Medical Director on a bi-weekly basis for review and further directions.

Await response from Medical Director for further instructions to proceed with the process of the audit findings. Audit materials and findings are not released until further directions from the Medical Director.

Per direction from the Medical Director, within 7 business days the auditor/internal reviewer will schedule an audit exit meeting with the Principal Investigator and/or key research staff. During the exit meeting, the auditor/internal reviewer will review the findings from the audit and discuss any corrective action(s) that may be necessary and may provide suggestions for best practice in study conduct, if necessary.

The Investigator/site will be offered assistance with the audit response form and any corrective action(s) required at this time if the response/corrective action plan can be completed on the same day of the exit meeting.

An audit report is composed and sent to the Principal Investigator. The Principal Investigator will have 7 business days to respond to how the significant finding(s) and any corrective action(s) will be addressed.

The response should include a plan of action to correct any problems identified and to prevent recurrences. A point-by-point response should include the suspected “root cause” of the issue, the individual(s) responsible for corrective action and response, and a timeline regarding the completion of the corrective actions.
The report and audit response will be duplicated. These along with an audit summary will be communicated to the GHS OHRP Medical Director for review and further direction. A summary of the audit findings and Investigator/site response with corrective action plan may be reported to the appropriate IRB at its monthly convened meeting.

Note that if the audit findings are not addressed in a timely manner, or not resolved to IRB satisfaction, the IRB can suspend or terminate the study in accordance with 45 CFR—Public Welfare — Department of Health and Human Services- Protection of Human Research Subjects—{CFR §46.113} and 21 CFR Part 56—Department of Health and Human Services - Food and Drug Administration (FDA) - Institutional Review Boards {CFR §56.113}.

A letter referencing the audit/internal review and findings as well as an audit certificate will be sent to the principal investigator following the review of all audit findings and/or audit response by the Medical Director.

Auditees will be solicited for feedback on the auditing process by means of direct contact with the Administrator in charge of the OHRP and/or questionnaire.

A memo referencing the audit date, Medical Director and/or IRB decision is placed in the IRB Files.

All audit reports will be secured in the Auditor’s/Internal Reviewer office.

5.0 THE AUDIT FINDINGS

The report will describe general audit finding trends and/or any extraordinary noncompliance found.

Based upon audit finding trends, new government agency regulations or guidelines, or new GHS/OHRP policies, the auditor/internal reviewer will provide ongoing education to research sites, investigators and staff.

If suspected or alleged noncompliance is reported to the Office of Human Research Protection or the GHS Office of Corporate Integrity, the OHRP auditor/internal reviewer may be sent on special assignment to investigate allegations.

The audit reports are internal and will not be voluntarily shared with outside agencies, unless the audit findings result in the termination or temporary suspension of a research project, in which case the IRB institutional official or representative will notify the appropriate regulatory agencies.

Other Compliance Responsibilities
If an investigator (researcher) or research associate(s) discover a serious compliance problem, the Office of Human Research Protection should immediately be contacted at (864)-455-8997.

When an investigator (research) receives notification of an upcoming compliance inspection visit by a regulatory agency, funding agency, or study sponsor, the IRB Coordinator should immediately be notified.

GHS OHRP Quality Improvement Strategies
• The auditor will randomly pull 20% of study records to review compliance of informed consent forms and documentation of continued voluntary participation.
• One measure of compliance includes assessing if all consent documents approved by the IRB in a set timeframe included all the required elements of disclosure.
• Audit results that show non-compliance with OHRP policies will be reviewed by GHS Corporate Compliance office, GHS OHRP Medical Director, and appropriate IRB Chairperson(s).

**Strategy for Improving Quality, Efficiency, and Effectiveness**
The GHS OHRP will look at measures of quality, efficiency, and effectiveness. One such measure evaluated by GHS OHRP includes surveying research staff regarding a recent IRB approval process experience. These evaluations and findings will be reported to the Institutional Official, GHS OHRP Medical Director and appropriate IRB Chairperson(s). Based on the findings of the evaluations, the IRB Chairs will work with the HRPP leadership to identify appropriate actions to be taken for improvement.

The above measures of compliance and quality, efficiency, and effectiveness will be taken and analyzed and provided to the OHRP Medical Director in order to direct improvements to the HRPP.

**FDA Inspection Compliance Responsibilities**
The investigator, or other authorized individual, with authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where drugs or devices are held.

The investigator, or other authorized individual, shall permit authorized FDA employees, at reasonable time and in a reasonable manner, to inspect, copy and verify all records relating to a study.

Upon notice that the FDA has reason to suspect that adequate informed consent was not obtained or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted, or are incomplete, inaccurate, false, or misleading, the investigator or other authorized individual shall permit authorized FDA employees to inspect and copy records that identify subjects.

**Applicable Regulations and Guidelines**

- **21 CFR 50** – Protection of Human Subjects
- **21 CFR 56** – Institutional Review Board
- **21 CFR 11** – Electronic Records and Signatures
- **21 CFR 312** – Investigational New Drug
- **21 CFR 812** – Investigational Device Exemptions
- **45 CFR 46** – Protection of Human Subjects
- **45 CFR 164** – Administrative Data Standards, Security and Privacy
- **ICH E6 - GCP** – Good Clinical Practice: Consolidated Guideline

**Inspection Readiness Guidance**
A guidance document to assist investigators in preparing for an inspection is available through the Office of Human Research auditor//internal reviewer. When appropriate, researchers will be given advanced notice of an upcoming inspection. However, some inspections can occur unannounced.
1.0 **SCOPE**

Federal regulations require that special considerations be given to protecting the welfare of particularly vulnerable subjects. In general, the regulations allow approval of research that is of minimal risk or that will benefit these subjects directly. However, the regulations require special safeguards, particularly with respect to obtaining informed consent.

2.0 **CHILDREN**

Children are defined as persons “who have not attained the legal age of consent to treatment or procedures involved in the research”. The GHS IRB generally considers all subjects under the age of 18 as children. Under South Carolina state law, participants must be at least 18 years of age to legally consent to participate in a research study. Any person claiming to be the “guardian” of a child must present a copy of the judicial order naming them as such in order to consent to participation in research for the minor.

All studies, which involve, or will potentially involve children must be identified by the PI at the time of submission of a protocol to the IRB. If children are to be added as study subjects after initial IRB approval, then the PI must submit an amendment describing how the children will be involved in the research and the potential risks to the subjects.

In all protocols involving children as subjects, the research must be classified into one of the four following categories. For those studies approved by full-convened board, the minutes must reflect the category under which the protocol was approved together with the protocol specific findings, which justify application of that category.

The four categories of research involving children are based on degree of risk and benefit of the individual subjects:

- **Category 1**: research involves no greater than minimal risk. (see Section II Relevant Definitions for definition of minimal risk);
- **Category 2**: research involves greater than minimal risk but presents the prospect of direct benefit to the individual subjects. Category 2 can only be approved if (1) the risk is justified by the anticipated benefit to the subjects and (2) the relation of the anticipated benefits to the risk is at least as favorable to the subjects as that presented by available alternative approaches;
- **Category 3**: research involves greater than minimal risk with no prospect of direct benefit to individual subjects. Category 3 research can only be approved if (1) the risk represents a minor
increase over minimal risk; (2) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations; and (3) the intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition which is of vital importance for the understanding of the subject’s condition;

- **Category 4:** research that does not fall into one of the three above categories, but which the IRB determines presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Research in this category cannot be approved by the IRB without the approval of the Secretary of HHS.

Only research in Category 1 can be approved by the Expedited Review process since research must present no more than minimal risk to qualify for Expedited Review.

**Note:** Studies involving children in schools will require approval of the school district(s) and parental permission. So as not to unnecessarily delay review and approval of a study, IRB applications and requests for district permission to conduct the study should, when allowed by the school district(s), be submitted simultaneously. The IRB will require that copies of district approval letters be uploaded with the IRB documentation.

### 2.1 Assent and Permission [45 CFR 46.408; 21 CFR 50.55]

In addition to permission of the parent(s) or guardian, assent to participate in the study must be obtained from each child age 12 years or older who, in the opinion of the investigator, is able to provide assent based on their age, maturity or psychological state. When the GHS IRB determines that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children involved in the research and the intervention or procedure is only available in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even when the children are capable of assenting, the GHS IRB may waive the assent requirement as described elsewhere in this document [Alteration or Waiver of Informed Consent, OHRP Policy No. 13.0 Section 5.0].

When obtained, assent must be documented in writing using the GHS IRB approved consent/assent form. When assent is not obtained, the investigator must document his/her rationale in the research records.

**Factors to take into consideration in determining whether to use assent form in children less than 12 years of age:**

1. Age, maturity and psychological state of the children involved.

Assent of children is not necessary for continuing with the clinical investigation, if the IRB determines that the capability of some, or all of the children, is so limited that they cannot reasonably be consulted; or

That the treatment or procedure involved in the clinical trial presents a prospect of direct benefit to the health or well-being of the children and is available only from the clinical trial.

### 2.2 Permission
After review of the research the IRB must determine whether the permission of one parent or two parents (or legal guardians) is required. For Categories 1 & 2 45 CFR 46.404 and 45 CFR 46.405, the permission of one parent is usually sufficient (although the IRB may, at its discretion, require the signature of both parents). For Categories 3 & 4 45 CFR 46.406 and 45 CFR 46.407 the permission of two parents is required (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).

2.3 Wards of the State

The GHS IRB does not review or approve research involving wards of the state.

2.4 When a Child Reaches the Age of Consent While Enrolled in a Study

Informed consent should be viewed as an ongoing process throughout the duration of a research project. When a child who was enrolled in research with parental or guardian permission subsequently reaches the age of consent (18 years old) to the procedures involved in ongoing research, the subject’s participation in the research is no longer regulated by the requirements of 45 CFR 46, Subpart D regarding parental or guardian permission and subject assent.

Unless the IRB determines that the requirements for obtaining informed consent can be waived, the PIs should seek and obtain legally effective informed consent as described in HRPP Policy 13.0 Informed Consent for any ongoing interactions or interventions with the subject. This is because the prior parental permission and child assent are not equivalent to legally effective informed consent for the now-adult subject. However, the IRB could approve a waiver of informed consent, if it finds and documents that the criteria for waiver are met.

Similarly, if the research does not involve any ongoing interactions or interventions with the subjects, but continues to meet the regulatory definition of “human subjects research” (e.g. continued analysis of specimens or data for which the subject’s identity is readily available to the PI), it would be necessary for the PI(s) to seek and obtain legally effective informed consent of the now-adult subjects. The IRB may consider, if appropriate, a waiver of the requirements for obtaining informed consent in order for the subjects to continue to participate in research.

3.0 PRISONERS

Federal regulations 45 CFR 46 Subpart C require that an IRB must be constituted with at least one member who participates in reviews who is a prisoner or prisoner representative in order for the IRB to review research involving prisoners as subjects. The GHS IRB does not currently have a member who is a prisoner or prisoner representative and therefore does not currently review research involving prisoners as subjects. A majority of the IRB (exclusive of prisoner members) have no association with the prison involved, apart from their membership on the IRB.

For prisoners, “minimal risk” means the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons. Furthermore, the regulations state that the IRB must find that the risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers (45 CFR 46.305(a)(3)).
The GHS IRB does not currently have a member who is a prisoner or prisoner representative and therefore does not currently review research involving prisoners as subjects.

If a participant is only incarcerated temporarily while enrolled in a study and the temporary incarceration has no effect on the study, then the prisoner is to be kept enrolled. If a participant is only incarcerated temporarily while enrolled in a study and the temporary incarceration has an effect on the study, then the situation should be handled according to the below guidance.

If a participant becomes a prisoner while enrolled in a research study that was not reviewed according to Subpart C, the IRB must confirm that the participant meets the definition of a prisoner (see Policy No. 3.0). If the participant is deemed a prisoner, it must be decided whether it is in the best interests of the participant to remain in the study or to terminate enrollment. It must also be decided whether it is feasible for the participant to remain in the study. If the participant remains in the study, it should be determined whether Subpart C applies to the participant. If Subpart C applies then an IRB must be found that can review the study or refer to the federal regulations and identify a prisoner representative so that the Greenville Health System’s IRB can review the study. If Subpart C does not apply to the participant, an IRB must be found that can review the study or develop written procedures for providing equivalent protections.

4.0 DECISIONALLY IMPAIRED PERSONS

The use of decisionally impaired persons as research subjects presents a risk that their disability may compromise their capacity to understand the information presented during the consent process and their ability to make a sound decision as to whether to participate in the research. For this reason the GHS IRB may make additional requirements to ensure protection of these subjects (e.g. assent, either verbal or written and documented in the study chart).

Determination of participants who are “decisionally impaired” will be made in accordance with GHS Policy Number S-50-31 Part IV Section B Adults.

Two physicians must certify the participant’s inability to consent and document the clinical reason for the inability to consent and the expected duration of the inability to consent. Surrogate decision makers will be located in accordance with the South Carolina Healthcare Consent Act and GHS Policy No. S-50-31 Part IV Section B Adults.

5.0 EDUCATIONALLY/ECONOMICALLY DISADVANTAGED

According to Federal regulations at 45 CFR 46.111(b), when some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as the educationally or economically disadvantaged, additional safeguards must be included in the study to protect the rights and welfare of these subjects. The IRB will review protocols that are likely to include educationally/economically disadvantaged subjects for the special risks that may be present for this group, i.e., the potential for undue influence/coercion in recruitment or enrollment, the potential for enrolling more subjects from this group than from other groups because of their vulnerability, etc.

6.0 STUDENTS, TRAINEES (e.g. MEDICAL RESIDENTS) AND EMPLOYEES

The GHS IRB aims to ensure that a subject’s decision to participate in research is truly voluntary and that there is no coercion for persons to participate in research. Students, medical residents, and
employees may be vulnerable to “subtle inducements to participate” in research by such methods as promises of academic rewards, professional achievement, vacation time, etc. Therefore, the GHS IRB requires that additional protections be in place in research studies where these persons will be recruited as subjects. Employees (normal volunteers) may not participate in immediate supervisor’s studies if the study poses greater than minimal risk. Exceptions are allowed for those who may derive direct health benefits (e.g. cancer protocol).

Generally, PIs who intend to recruit students, employees, or medical residents as subjects are required to clearly define the subjects to be enrolled, the rationale for their participation and the proposed method for their recruitment. Students and employees should not be the sole recruitment target unless the research objective is to study this population. The Institutional Official must be notified of the proposed research use of the medical residents and employees as subjects and must provide written approval to the IRB. Employees directly employed by the PI or co-PIs may not be used as subjects without the expressed permission of the IRB. Due to the increased risk of loss of confidentiality, the PI must also explain in the protocol the methods to be used to protect these subjects’ identities in the research data.
Greenville Health System (GHS) may rely on the IRB of another institution or organization, or an independent IRB for review and approval of human research if such reliance benefits GHS and its investigators. The GHS Institutional Official has the ultimate authority regarding whether or not to rely on the IRB of another institution or organization, or an independent IRB. When relying on the IRB of another institution or organization, or an independent IRB, GHS remains ultimately responsible for the protection of human subjects in all covered research in which GHS engages.

**Investigator Responsibilities**

1. For initial review the GHS investigator will provide the GHS IRB with a copy of:
   - The letter of approval from the reviewing IRB
   - The final approved protocol and informed consent
   - The grant, if applicable
   - All relevant IRB minutes documenting the review and approval of the study (if requested)
   - Any other documents considered by the IRB in making its determination to approve the study

2. For continuing review the GHS investigator will provide a copy of:
   - The continuing review approval letter from the reviewing IRB
   - The final approved protocol and informed consent
   - The Progress Report
   - All relevant IRB minutes documenting the review and approval of the study (if requested)
   - Any other documents considered by the IRB in making its determination to approve the study

3. For modifications or amendments the GHS investigator will provide a copy of:
   - The proposed modification or amendment
   - Documentation from the reviewing IRB of approval of the modification or amendment
   - The modified or amended protocol, consent form or other study documents
   - All relevant IRB minutes documenting the review and approval of the study (if requested)

4. For unanticipated events involving risks to subjects or others
• Any unanticipated events involving risks to subjects or others must be reported according to GHS policy

5. For closure of the study
• Once research is completed, the GHS investigator must submit a final report to close the study

Responsibilities of the Reviewing IRB

1. For studies conducted or supported by any federal department or agency that has adopted the Federal Policy for the Protection of Human Subjects, known as the Common Rule, the reviewing IRB will comply with the terms set forth in the Code of Federal Regulations at 45 CFR 46 (including Subparts A, B, C, and D), unless the research is otherwise exempt from these requirements, or the department or agency conducting or supporting the research has determined that the research shall be covered by a separate assurance.

For clinical investigations regulated by FDA under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)), the reviewing IRB will apply FDA human subjects regulations. These regulations include, but are not limited to Protection of Human Subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), Investigational Drugs (21 CFR 312), Investigational Devices (21 CFR 812), and Application for FDA Approval to Market a New Drug (21 CFR 314).

For all other research involving human participants the reviewing IRB will be guided by the Code of Federal Regulations at 45 CFR 46. In addition, except where in conflict with 21 CFR 56, GHS applies the International Conference on Harmonization (ICH) Good Clinical Practice Consolidated Guidelines (1996) for all research involving human participants regardless of funding source or oversight agency.

2. Upon request, the reviewing IRB will make available to GHS relevant minutes of its meetings and any other documents related to the review, approval and continuing oversight of the research study.

3. The reviewing IRB will provide prompt notification of all actions, requirements and determinations it makes related to the participation of GHS in the research study.

Responsibilities of GHS

1. Designate a GHS IRB Chair to perform a facilitated review of the research protocol and the external IRB's decisions and determinations to ensure that:
   • The GHS investigators and staff conducting the research are appropriately qualified
   • The study meets GHS standards
   • Other applicable institutional approvals, such as Investigational Drug Pharmacy, Radiation Safety and Biosafety have been obtained before research begins
   • Those actions and determinations made by the reviewing IRB meet GHS standards for initial review, continuing IRB review or review of modifications to previously approved research
   • No concerns about local context are present
   • The consent form complies with GHS standards and requirements
   • The consent form contains applicable GHS standard language
2. Promptly report to the reviewing IRB and as applicable to the Office for Human Research Protections (OHRP), Food and Drug Administration (FDA), study sponsor and to all other appropriate agencies and individuals:
   • Any unanticipated problems involving risks to subjects or others
   • Any serious or continuing noncompliance with the determinations of the GHS IRB or reviewing IRB
   • Any suspension or termination of approval
3. Make available to the reviewing IRB relevant minutes of meetings and any other documents related to the approval, conduct, monitoring or oversight of this research study, as requested.

Possible Review Determinations

1. GHS retains the authority to accept the reviewing IRB’s approval, or to make minor changes through the GHS “facilitated review”, or to require review by a convened GHS IRB.
2. The GHS IRB Chair will either:
   • Accept the reviewing IRB approval
   • Accept the reviewing IRB approval with minor modifications
   • Not accept the reviewing IRB approval and refer the study to a convened GHS IRB for review
3. If the reviewing IRB approval is accepted, the investigator will be sent written notification by the GHS IRB that the reviewing IRB approval is affirmed.
1.0 INTRODUCTION

Pursuant to the federal regulations on human subjects research (45 CFR 46, the Common Rule), the Institutional Review Board (IRB) was created. Greenville Health System (GHS) maintains a Federalwide Assurance (FWA) with the Department of Health and Human Services (DHHS), which requires that all human subjects research, whether funded or not, be conducted at or on behalf of the institution be reviewed and approved by an IRB prior to initiating a research study.

As an alternative model of IRB review, proposed research protocols which will be conducted at GHS and meet specified criteria may be submitted to the Western Institutional Review Board (WIRB) for review and approval. GHS will be responsible for selecting which industry sponsored studies will be submitted to the WIRB. A negotiated Agreement between GHS and WIRB is on record, and GHS is assured that WIRB is qualified to review local research pursuant to the “Program by Greenville Health System and Western Institutional Review Board to Assure WIRB Knowledge of Local Research Context” found in Exhibit A of the Agreement.

2.0 OBJECTIVES

The objective of this SOP is:

2.1 Describe the documentation requirements and submission procedures for eligible proposed research protocols requesting that WIRB serve as the IRB of record for research involving human subjects.

2.2 Outline the process of approval for submission to WIRB by the GHS Office of Human Research Protection.

2.3 Identify the documentation and review responsibilities of the GHS IRB for WIRB-approved protocols.

3.0 SCOPE

These policies and procedures apply to principal investigators conducting human subjects research who have requested centralized IRB review by WIRB.

4.0 POLICIES AND ASSOCIATED PROCEDURES

4.1 Eligibility Requirements of Proposed Research Protocols
4.1.1 In order to utilize the WIRB services, the proposed research protocol must meet several criteria:

4.1.1.1 The protocol must meet the NIH definition of a clinical trial.

4.1.1.2 The protocol must be industry-sponsored and must have been designed and written by the industry sponsor.

4.1.1.3 The industry sponsor must hold all INDs/IDEs for the protocol, where applicable.

4.1.1.4 The protocol must be a Phase II/III/IV clinical trial designed to evaluate prospectively the safety and/or effectiveness of new drugs or biologics.

4.1.1.5 The GHS investigator has not previously submitted the study to a GHS IRB.

4.1.1.6 The GHS IRB charges a one-time fee for the processing of industry-sponsored protocols submitted to the Western IRB for review. The contract agreement will include this fee to be paid to the GHS by the sponsor.

4.1.2 The following protocols are not eligible for review by WIRB:

4.1.2.1 Investigator-initiated clinical trials regardless of funding;

4.1.2.2 Protocols receiving funds from a federal or other not-for-profit funding agency;

4.1.2.3 Protocols with industry sponsors who refuse to pay commercial and local IRB fees;

4.1.2.4 Studies involving special local, social, economic, political, or cultural concerns, including but not limited to xenotransplantation, gene transfer, and/or embryonic stem cells;

4.1.2.5 Protocols requiring emergency use/review;

4.1.2.6 Protocols involving medical devices, including those subject to HUD/IDE regulations;

4.1.2.7 Protocols requiring review and approval by the GHS Biosafety Committee (e.g. the study involves recombinant DNA);

4.1.2.8 Research requesting waivers of informed consent and authorization; or

4.1.2.9 Research involving children.

4.2 Division of Responsibilities Between the GHS IRB and WIRB
4.2.1 The following division of responsibilities is based on the premise that the WIRB’s primary function is initial and continuing review of human subject research protocols and that the GHS IRB’s primary function is determination of eligibility for submission to WIRB and limited local oversight.

4.2.2 The responsibilities of the WIRB are to:

4.2.2.1 Perform initial reviews of proposed research protocols, identify and discuss any issues, and make a final decision of approval or disapproval of the protocol.

4.2.2.2 Carry out continuing reviews and reviews of serious adverse events, protocol amendments, DSMB reports, subject complaints/allegations, and any other documents submitted by the PI for all GHS protocols reviewed by WIRB.

4.2.2.3 Notify the GHS IRB that WIRB has accepted review of proposed research protocols, and provide the GHS IRB with regular reports of studies for which WIRB is the IRB of record.

4.2.2.4 Maintain relevant communication with the PI regarding all approvals and denials regarding the protocol.

4.2.2.5 Maintain a Board membership that satisfies the requirements of 45 CFR 46, 21 CFR 56 and provides special expertise as needed from Board members or consultants to adequately assess all aspects of each protocol including local context issues.

4.2.3 The responsibilities of the GHS IRB are to:

4.2.3.1 Determine eligibility of proposed research protocols for review by WIRB based on the criteria listed in Section 4.1 above.

4.2.3.2 Ensure that all investigators and staff are properly qualified and meeting GHS IRB standards for eligibility to conduct research, including but not limited to human subjects protection training and collection and maintenance of conflict of interest disclosure forms.

4.3 Review and Approval Process

4.3.1 The local institution PI or designee will complete all required IRB documentation from the GHS IRB website. The local institution PI or designee will then submit all required documentation related to the protocol for review to the Office of Human Research Protection via electronic submission.

4.3.1.1 Documentation should include, but is not limited to:

4.3.1.1.1 GHS Application for Protocol Review by WIRB;

4.3.1.1.2 GHS Request for Submission Form to WIRB
4.3.1.3 WIRB Initial Submission Form or Investigator Submission Form for Multi-Center Protocols;

4.3.1.4 Curriculum vitae (CVs) for all investigators

4.3.1.5 IRB application materials including but not limited to research protocol, informed consent statement, authorization form, drug brochure, advertisements and solicitation scripts, if applicable;

4.3.1.2 The PI and research staff should note that the informed consent form(s) which are submitted with the protocol must conform to GHS IRB and WIRB approved language and standard statements.

4.3.1.2.1 Local additions to the informed consent template dealing with contact information shall be added.

4.3.1.2.2 WIRB may also request substitutions or additions in the informed consent template, particularly to facilitate comprehension by the local population, as long as the proposed changes do not alter the meaning of the content.

4.3.2 Upon receipt of required documentation, GHS IRB staff will review the application for eligibility of review by WIRB and, if eligible, will forward to the GHS OHRP Medical Director for approval to submit to WIRB.

4.3.3 Notification of WIRB review eligibility will be communicated to the PI via eIRB.

4.3.3.1 If eligibility is denied, GHS IRB staff will notify the PI and request that the study be resubmitted via the formal GHS IRB process.

4.3.3.2 If eligibility is approved, the GHS IRB staff will notify the PI that he/she may proceed with the initial submission documentation to WIRB via the WIRB online submission process.

4.3.3.3 After submission to WIRB, all protocol correspondence will take place directly between WIRB and the PI.

4.3.3.4 Upon notification of approval from WIRB, the protocol investigators and staff will utilize only WIRB-approved documents.

4.3.4 For any WIRB protocol, regardless of its disposition, the GHS IRB will maintain an electronic copy of the protocol file, via the eIRB. These documents shall be
retained in accordance with GHS OHRP Policies and Procedures and federal requirements.

4.3.5 GHS IRB may not approve research which has been disapproved by WIRB; however, GHS IRB may disapprove any study approved by WIRB. Despite this right, the GHS IRB will use its best efforts to ensure that clinical research will be performed in accordance with WIRB decisions.
**INTRODUCTION**

The Greenville Health System’s IRB (GHS IRB) is a participating member of the National Cancer Institute’s Central Institutional Review Board (NCI CIRB) initiative. The GHS IRB has agreed to a division of responsibilities based on the premise that the NCI CIRB’s primary function is initial and continuing review of adult and pediatric Phase 2 and Phase 3 clinical trials and that the local institution’s primary function is consideration of local context and oversight of local performance for these protocols.

Investigators intending to conduct a study for which the NCI CIRB can serve as the IRB of record must undergo local review to ensure compliance with institutional requirements that are not assessed by the CIRB’s Local Context Subcommittee. This local review will be conducted by the GHS IRB Chair(s).

**Specific Policies**

1.1 **Division of Responsibilities Between the NCI Central IRB and GHS IRB**

1.1.1 The following division of responsibilities is based on the premise that the CIRB’s primary function is initial, and continuing, review of adult and pediatric research protocols and that the local institution’s primary function.

1.1.2 The responsibilities of the CIRB are:

- **1.1.2.1** Maintain an NCI CIRB membership that satisfies the requirements of 45 CFR 46 and 21 CFR 56 and provides special expertise as needed to adequately assess all aspects of each study; a) post the roster of NCI CIRB membership on the public side of NCI CIRB website;

- **1.1.2.2** Conduct initial, amendment, and continuing review of studies as well as review of any other study-specific documents submitted by the Study Chair to the NCI CIRB;

- **1.1.2.3** Conduct review of local context considerations: as outlined in the following Worksheets: the Annual Signatory Institution Worksheet About Local Context for NCI CIRB Review, the Annual Principal Investigator Worksheet About Local Context, and the Study-Specific Worksheet About Local Context;

- **1.1.2.4** Conduct review of potential unanticipated problems and/or serious or continuing noncompliance when the Signatory Institution or other entity reports an incident, experience, or outcome to the CIRB. This review includes the following step: report any unanticipated problem and/or serious or continuing noncompliance determination to OHRP, the FDA, and the NCI Signatory Official;

- **1.1.2.5** Conduct review of individual Adverse Event Reports for studies without a Data and Safety Monitoring Board (DSMB) or equivalent monitoring body;

- **1.1.2.6** Post all study-specific documents related to CIRB reviews to the restricted access side of the CIRB website; Notify research staff and institutional designees of all CIRB actions, per written procedures, via institution-specific correspondence, broadcast emails, and access to the restricted area of the CIRB website;

- **1.1.2.7** Notify the Signatory Institution immediately if there is ever a suspension or restriction of the CIRB’s authorization to review a study; and
1.1.2.8 Post the NCI CIRB Standard Operating Procedures on the public side of the CIRB website.
1.1.3 The responsibilities of the Signatory Institution are to:

1.1.3.1 Comply with the NCI CIRB’s requirements and directives;

1.1.3.2 Report to the NCI CIRB the names of any Component or Affiliate Institutions that rely on the Signatory Institution’s IRB.

1. Component Institutions are defined by the NCI CIRB as meeting all of the following criteria:

   a) the Component Institution operates under a different name than the Signatory Institution, but the Signatory Institution has legal authority for the Component Institution;

   - the FWA number for the Component Institution is the same as the Signatory Institution;

   - the local context considerations of the Component Institutions are the same as the Signatory Institution. Local context considerations are reported by the Signatory Institution in the Annual Institution Worksheet About Local Context; and

   - the conduct of research at the Component Institution is monitored by the same office as the Signatory Institution.

   b) Affiliate Institutions are defined by the NCI CIRB as meeting all of the following criteria:

   - the local context considerations of the Affiliate Institution are the same as the Signatory Institution. Local context considerations are reported by the Signatory in the Annual Institution Worksheet About Local Context;

   - the boilerplate language and institutional requirements of the Affiliate Institution are the same as the Signatory Institution. The boilerplate language and institutional requirements are reported by the Signatory Institution in the Annual Institution Worksheet About Local Context; and

   - the conduct of research at the Affiliate Institution is monitored by the same office as the Signatory Institution.

1.1.4 Ensure the safe and appropriate performance of the research at the Signatory Institution and all Components and Affiliates. This includes, but is not limited to:

   a) ensuring the initial and ongoing qualifications of investigators and research staff;

   b) overseeing the conduct of the research;

   c) monitoring protocol compliance;

   d) maintaining compliance with state, local or institutional requirements related to the protection of human subjects;

   e) providing a mechanism to receive and address concerns from local study participants.
participants and others about the conduct of the research;

f) investigating, managing, and providing notification to the NCI CIRB of any study-specific incidence, experience, or outcome that seems to rise to the level of an unanticipated problem and/or serious or continuing noncompliance, the institution must provide a plan to manage the incident, experience, or outcome, including measures to prevent similar occurrences;

NOTE: As part of ensuring safe and appropriate performance of research the Signatory Institution has the authority to observe any aspect of the research process including observing the consent process. The CIRB retains the authority to direct this to be done when necessary.

1.1.5 Provide updates in a timely manner to the NCI CIRB whenever a Signatory Institution Principal Investigator is no longer the responsible party for a study under the purview of the NCI CIRB;

1.1.6 Notify the NCI CIRB when a regulatory deficiency has been cited on an audit that occurred during the time that the NCI CIRB was responsible for study review;

1.1.7 Complete and submit the Annual Institution Worksheet About Local Context, the Annual Investigator Worksheet About Local Context, and any other worksheets/forms required by the NCI CIRB for participation;

1.1.8 Decide on a study-by-study basis whether to open the study through the NCI CIRB or to conduct its own local IRB full Board review. Indicate the decision to open a study through the NCI CIRB by submitting a Study –Specific Worksheet About Local Context;

1.1.9 In the local consent form:
   a) incorporate NCI CIRB-approved boilerplate language into the NCI CIRB-approved model consent form;

   NOTE: Including HIPAA Authorization language as part of boilerplate language is permitted. The CIRB does not approve the HIPAA Authorization language as it does not function as a Privacy Board however the CIRB will accept HIPAA Authorization language when submitted as part of the boilerplate.

   b) make no language changes to the consent form with the exception of NCI CIRB-approved boilerplate language;

   c) obtain NCI CIRB approval of changes to the boilerplate language prior to implementation;

   d) obtain NCI CIRB approval of translations of the consent form prior to implementation.

1.1.10 Maintain regulatory file for each study under NCI CIRB purview as per local institution and sponsor policy;
1.2 Independent Review Process

1.2.1 The purpose of the local IRB Chair review is to determine whether any local context issues exist which would suggest that local IRB review and oversight should be required.

1.2.2 The PI must conduct all procedures in accordance with NCI CIRB policy (www.ncicirb.org)

1.2.3 The following items should be submitted to the local IRB via the eIRB Module(s) (Continuing Review; Amendments; Reportable Events):

   1.2.3.1 All new studies which are approved by the CIRB, including approval letter, that will be conducted locally. The GHS OHRP staff will verify all CITI training for all research personnel listed on the study is current;

   1.2.3.2 NCI CIRB approval letter at continuing review will be uploaded as a Public Comment via the eIRB Continuing Review module within thirty (30) days of the broadcast memo;

   1.2.3.3 Amendment/Modification reviews will be completed by the NCI CIRB. If a study is closed to enrollment, the NCI CIRB will notify the study team if they should use a revised consent form or an addendum they provide to re-consent the patient(s). No documentation is required by the GHS IRB. 

   NOTE: The only exceptions to this are:
   - change in PI;
   - change in recruitment section that would require a new HIPAA waiver.

   The following are the only types of amendments that should be submitted to the GHS IRB for review and approval via the eIRB:
   1. Personnel Changes: Submit all personnel changes using the eIRB system;
   2. Addition of a site that is not affiliated with GHS;
   3. All advertisements, created locally, will be submitted via the eIRB amendment module as well as submitted to NCI CIRB. All other advertisements will be reviewed by the NCI CIRB.

   NCI CIRB approval letter for all amendments will be uploaded as a Public Comment via the eIRB Amendment module within thirty (30) days of the broadcast memo;

   1.2.3.4 NCI CIRB approval/acknowledgement letters for all reportable events will be uploaded as a Public Comment via the eIRB Reportable Events module within thirty (30) days of receipt of the broadcast memo. Local unanticipated problems, local unanticipated deaths, and local subject complaints must be entered into the eIRB Reportable Events module upon notification from the PI/study nurse.

1.2.4 Local IRB review of new studies may result in one of three decisions:
1.2.4.1 Approved as submitted. The NCI CIRB Independent review process is accepted. The NCI CIRB will be designated as the IRB of Record and is responsible for the duties outlined above.

1.2.4.2 Approved with provisions. The IRB Chair, or member, is suggesting provisions to the submission and the submission may be finally approved after a response to such provisions is accepted. Upon final approval, the CIRB will be designated the IRB of record and is responsible for the duties outlined above.

1.2.4.3 Not approved. This protocol must undergo full board review and is not accepted for NCI CIRB Independent review. Full GHS IRB oversight is required.

2. SCOPE

These policies and procedures apply to all CIRB-approved research that the GHS IRB has deferred oversight to through the NCI CIRB.
## Appendices

**Appendix A:** Reportable Event Reporting Requirements

**Appendix B:** Institutional Review Committee (IRB) Language Services

**Appendix C:** Institutional Review Board (IRB) Non-Compliance Reviewer Form

**Appendix D:** Planned Emergency Research Form-Research Subject to FDA Regulations

**Appendix E:** Checklist for Studies Involving Federal Funding Department of Defense (DoD)
Reportable Event Reporting Requirements – Appendix A

EXTERNAL Events:
All events for Phase I studies must be submitted individually as they are received by the site. These will be scheduled for review at a convened meeting.

Except for Phase I studies, only events meeting the definition of an unanticipated problem are to be submitted individually as they are received by the site. All others must be submitted as a cumulative report at the time of continuing review (via upload in ‘general comments’).

Except for Phase I studies, any external event which is not defined as an unanticipated problem but is submitted anyway will no longer be acknowledged by the IRB/IRB staff. Rather, the ‘not reportable’ option in eIRB will be chosen.

INTERNAL Events:
All events for Phase I studies must be submitted as they occur. These will be scheduled for review at a convened meeting.

Except for Phase I studies, only events which meet all three of the following criteria are to be submitted as they occur and will be scheduled for review at a convened meeting:

Unexpected and Serious and Related/Possibly Related.

All others must be submitted as a cumulative report at the time of continuing review (via upload in ‘general comments’).

Reporting Requirements for INTERNAL DEATHS and HOSPITALIZATIONS if Related or Possibly Related to the Study are required to be reported.

All internal deaths during the study or 90 days post termination from study intervention, are required to be reported as adverse events (see HRPP Policy 18.0 Section 5.0)
GREENVILLE HEALTH SYSTEM
Institutional Review Committee (IRB) Language Services Form – Appendix B

Study Title:

Principal Investigator: ____________________________________________________

IRC File # ______________      Date of IRC-Approved Consent Form: ____________

IRC Review Type:  □ New Study      □ Reapproval      □ Revision/Amendment
                  □ Other (specify): __________________________________________

Study Funding:    □ GHS (Grant, Investigator Initiated or resident)
                  □ Industry Sponsored
                  Account to be charged by Interpretive Services: __________________

Check ONE: □ Translated English to __________________ (list language or
languages) [IRC-Approved English Version Provided]

□ Provided Review for Accuracy Only (________________ &
               English Versions Provided)

The attached consent form for the above-mentioned study is an accurate translation of the IRC-
approved consent form. The translation/review was performed by GHS Language Services
Translation Team utilizing the services of a physician prior to final review by the GHS Language
Services Translation Team.

GHS Language Services Translation Team Member                                      Date

Manager of Language Services                                                        Date

This form must be returned completed and signed to the IRB office,
along with the translated consent form, prior to review by the IRB.

REVISION 5: 5/29/09
GREENVILLE HEALTH SYSTEM
Institutional Review Board (IRB) Non-Compliance Reviewer Form

Reviewer: 

Protocol #: 

PI: 

Level of Study Risk: □ Minimal Risk □ More than Minimal Risk

Category of Initial Review: □ Expedited □ Full Board

Type of Non-Compliance: □ False Allegation □ Serious
□ Continuing □ Neither Serious nor Continuing

Please use this checklist for reference when reviewing this non-compliance case. Make notes in the space provided. Please contact the PI with any questions.

OHRP office to complete Summary and Items 1-5

SUMMARY/GENERAL COMMENTS

1. Please indicate the nature of the non-compliance.

□ Deviated from approved protocol
□ Failed to follow IRB procedures
□ Failed to protect participants’ rights
□ Other: ______________________________

2. Please list non-compliance history for PI, Co-PI.

3. Please list PI, Co-PI training type(s) and date(s).

4. How was this event reported to the IRB?

5. What steps, if any, did the investigator take to rectify the non-compliance?
ITEMS 6-9 TO BE COMPLETED BY NON-COMPLIANCE COMMITTEE MEMBER REVIEWER

6. Implications for risk to participants:

7. Implications for informed consent process:

8. Implications for the training of researchers:

9. Please list your recommendations for how to resolve this non-compliance case below:
   - Modifying the research protocol;
   - Modifying the consent process;
   - Contacting past or current participants with additional information;
   - Re-consenting participants;
   - Modifying the approval period;
   - Suspension;
   - Termination;
   - Utilizing the Peer Review Process;

Recommendations:
GREENVILLE HEALTH SYSTEM
PLANNED EMERGENCY RESEARCH FORM
RESEARCH SUBJECT TO FDA REGULATIONS

1. Describe how study subjects are in a life-threatening situation, and how available treatments, if any, are unproven or unsatisfactory.

2. Why is the collection of scientific evidence, which may include evidence related to placebo-controlled investigations, necessary to determine the safety and effectiveness of the test article?

3. Informed consent is not feasible because: (check all that apply)
   - The subjects will not be able to give their informed consent as a result of their medical condition;
   - The test article must be utilized before consent from the subject’s legally authorized representative is feasible;
   - There is no reasonable way to prospectively identify the individuals likely to become eligible for participation in the clinical investigation.

4. Participation in the study may result in direct benefit to the patient because:
   - Subjects are facing a life-threatening situation that necessitates intervention;
   - Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
   - Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
5. Can the research proceed without the waiver of consent?
   O Yes  O No

6. Describe how you will attempt to contact a legally authorized representative to obtain consent. How will you document your efforts?

7. Have you submitted an Informed Consent Form to the IRB for approval?
   O Yes  O No

8. How will you document?
   o Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

   o Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for investigation and its risks and expected benefits;

   o Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research populations, and its results;
o Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

o If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject’s family member who is not a legally authorized representative, and asking whether he or she objects to the subject’s participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

______________________________________________
Printed Name of Investigator

______________________________________________
Signature of Investigator Date
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<tbody>
<tr>
<td>1.</td>
<td>Is the research classified? (classified research cannot be approved by the IRB)</td>
<td>Yes</td>
<td>No</td>
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| 2. | Initial and continuing research education has been completed for all personnel who conduct, review, approve, oversee, support, or manage human participants research.  
   - DoD program – specific educational requirements have been completed?  
| 3. | Does the research have scientific merit (or outside experts have provided an evaluation of scientific merit and the IRB concurs)? | Yes | No |
| 4. | Do consent documents disclose provisions for research-related injury and follow the requirements of the DoD component? | Yes | No | N/A |
| 5. | Does the research involve an “experimental subject”? | Yes | No | N/A |
| 6. | If the PI is requesting a waiver of consent, does the PI have an approved waiver from the Secretary of Defense? | Yes | No | N/A |
| 7. | Has a research monitor been appointed?  
   - Required for research involving greater than minimal risk.  
   - Required for a portion of research or studies involving no more than minimal risk  
   NOTE: “Minimal Risk” is defined as hazards ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests. However, the risks imposed in research involving human subjects focused on a special population should note be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone). | Yes | No | N/A |
| 8. | Has the research monitor been appointed by name and is the monitor independent of the team conducting the research?  
   - There may be more than one research monitor (e.g. if different skills or experience are needed.  
   - The may be an ombudsman or a member of the data safety monitoring board.  
   - The IRB must approve a written summary of the monitors’ duties, authorities, and responsibilities. | Yes | No | N/A |
| 9. | Has the IRB or HRPP official communicated with research monitors to confirm their duties, authorities, and responsibilities? | Yes | No | N/A |
| 10. | Have the duties of the research monitor been determined on the basis of |   |   |   |

This checklist is designed to support the Principal Investigator (PI) and the IRB reviewer in evaluation of protocols funded by the Department of Defense (DoD).
specific risks or concerns about the research?  
**Research monitors:**  
- May perform oversight functions (e.g. observe recruitment, enrollment procedures, and the consent process, oversee study interventions and interactions, review monitoring plans and unanticipated problems involving risks to participants or others, oversee data matching, data collection and analysis).  
- May discuss the research protocol with researchers, interview human subjects, and consult with others outside of the study.  
- Report observations and findings to the IRB or a designated official.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
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<tr>
<td>11. If the research is greater than minimal risk, has the PI identified a DoD required “Research Monitor” with authority to:</td>
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<td>- Stop research in progress;</td>
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<td>- Remove individuals from the study; and</td>
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<td>- Take any steps necessary to protect the safety and well-being of the subjects until the IRB can assess the monitor’s report?</td>
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<td>12. Does the DoD funded Research involve vulnerable populations?</td>
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<td>For the purposes of applying Subpart B, the phrase “biomedical knowledge” shall be replaced with “generalizable knowledge”.</td>
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<td>The applicability of Subpart B is limited to research involving pregnant women as participants in research that is more than minimal risk and included interventions or invasive procedures to the woman or the fetus or involving fetuses or neonates as participants.</td>
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<td>Fetal research must comply with US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g</td>
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<td>13. Does the study involve International research?</td>
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<td>- The researcher has documented that permission has been granted to conduct research in that country by certification, or local ethics review?</td>
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<td>- The researcher has documented how he/she will identify and follow all local laws, regulations, customs, and practices.</td>
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<td>14. Does the research involve U.S. military personnel?</td>
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<td>If “Yes”, the IRB must determine the research does not involve undue influence.</td>
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<tr>
<td>- Officers are not permitted to influence the decision of their subordinates.</td>
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<td>- Officers and senior non-commissioned officers may not be present at the time of recruitment.</td>
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<tr>
<td>- Officers and senior non-commissioned officers have a separate opportunity to participate.</td>
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• When recruitment involves a percentage of a unit, an independent ombudsman is present.

15. If the research includes military personnel as participants, does the protocol incorporate additional safeguards to minimize undue influence from individuals within potential participant’s chain of command?

   □ Yes □ No □ N/A

16. If the research includes military personnel as participants, do the policies and procedures require limitations on dual compensation?
   • Prohibit an individual from receiving pay of compensation for research during duty hours.
   • U.S. military personnel may be compensated for research if the participant is involved in the research when not on duty.
   • Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to $50 for each blood draw.
   • Non-Federal persons may be compensated for research participation other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.

   □ Yes □ No □ N/A

Additional Considerations for the PI and the IRB

1. Any the following must be promptly reported (within 7 working days) to the DoD human research protection officer:
   • Any determinations of serious or continuing non-compliance of DoD supported research.
   • When significant changes to the research protocol are approved by the IRB.
   • The results of the IRB continuing review.
   • Change of reviewing IRB.
   • When the organization is notified by the Federal department, agency or national organization that any part of the HRPP is under investigation for cause involving DoD-supported research.
   • Any unanticipated problems involving risks to participants or others for any Department of Defense (DoD)-supported research.
   • Any suspension of DoD-supported research.

2. Surveys performed on Department of Defense personnel must be submitted, reviewed, and approved by the Department of Defense after the research protocol is reviewed and approved by the IRB.
   • For any DoD-supported investigator, the following shall be promptly (within 7 working days) reported to the DoD human research protection officer:
     o When significant changes to the research protocol are approved by the IRB.
     o The results of the RIB continuing review.
     o Change of reviewing IRB.
     o When the organization is notified by any Federal department, agency, or national organizations that any part of an HRPP is under investigation for cause involving DoD-supported research protocol.

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

4. When the researcher is conducting multi-site research, a formal agreement exists between organizations to specify the roles and responsibilities of each party.

5. Consent documents disclose provisions for research-related injury following the requirements of the Department of Defense component.
6. **Experimental subject (research involving a human being as an experimental subject):** An activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Research involving a human being as an experimental subject is a subset of research involving human subjects. This definition relates only to the application of section 980 of Reference (g); it does not affect the application of part 219 of Reference (c). This definition does not include activities that are not considered research involving human subjects, activities that meet the exemption criteria at section 219.101(b) of Reference (c), and research involving the collection or study of existing data, documents, records, or specimens from living individuals.

- If the research subject meets the definition of “experimental subject”, prohibit a waiver of the consent process unless a waiver is obtained from the Assistant Secretary of Defense for Research and Engineering.
- The Assistant Secretary of Defense for Research and Engineering may waive the requirements for consent when all of the following are met:
  - The research is necessary to advance the development of a medical product for the military services.
  - The research may directly benefit the individual experimental subject.
  - The research is conducted in compliance with all other applicable laws and regulations.

If the research subject does not meet the definition of “experimental subject”, the IRB is allowed to waive the consent process.

7. If consent is to be obtained from the experimental subjects’ legal representative, the research must intend to benefit the individual subject. Determination that research is intended to be beneficial to the individual experimental subject must be made by the IRB.

8. If a participant becomes a prisoner, if the researcher asserts to the IRB that it is in the best interest of the prisoner-participant to continue to participate in the research while a prisoner, the IRB chair may determine that the prisoner-participant may continue to participate until the convened IRB can review this request to approve a change in the research protocol and until the Greenville Health System official and DoD Component office review the IRB’s approval to change the research protocol. Otherwise, the IRB chair shall require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened IRB can review this request to approve a change in the research protocol. The convened IRB, upon receipt of notification that a previously enrolled human participant has become a prisoner, shall promptly review the research protocol to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert having the expertise of a prisoner representative if the IRB reviewing the research protocol does not have a prisoner representative. If the prisoner-participant can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-participant’s confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human participants from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-participant to continue to participate in the research. This approval is limited to the individual prisoner-participant and does not allow requirement of prisoners as participants.

- Research involving a detainee as a human participant is prohibited.
- This prohibition does not apply to research involving investigational drugs and devices when the same products would be offered to U.S. military personnel in the same location for the same condition.
- The exemption for research involving survey or interview procedures or observation of
public behavior, does not apply to research with children, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

| 9. | The IRB is aware of the definition of “prisoner of war” for the DoD component granting the addendum. |

**Notes:**

1. Research involving Prisoners of War is prohibited