b. determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since the previous IRB review; and
c. 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 apparent immediate hazards to the subjects.

Upon request, the Institution will provide a copy of these written procedures to OHRP or any U.S. federal department or agency conducting or supporting research to which the FWA applies.

v. Institutional Support for the IRB(s)

The Institution will ensure that each IRB upon which it relies for review of research to which the FWA applies has meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

vi. Reliance on an External IRB

Whenever the Institution relies upon an IRB operated by another institution or organization for review of research to which the FWA applies, the Institution must ensure that this arrangement is documented by a written agreement between the Institution and the other institution or organization operating the IRB that outlines their relationship and includes a commitment that the IRB will adhere to the requirements of the Institution's FWA. OHRP's sample IRB Authorization Agreement may be used for such purpose, or the parties involved may develop their own agreement. This agreement must be kept on file at both institutions/organizations and made available upon request to OHRP or any U.S. federal department or agency conducting or supporting research to which the FWA applies.

vii. Renewal or Update of the Assurance

The Institution must renew its FWA every 5 years, even if no changes have occurred, in order to maintain an active FWA.

The Institution must update its FWA within 90 days after changes occur regarding the legal name of the Institution, the Human Protections Administrator, or the Signatory Official.

Any renewal or update that is submitted to, and accepted by, OHRP begins a new 5-year effective period.

Failure to renew or update an FWA appropriately may result in restriction, suspension, or termination of OHRP's approval of the Institution's FWA.

1.2 OVERVIEW OF ETHICAL PRINCIPLES AND REGULATIONS GOVERNING THE PROTECTION OF HUMAN SUBJECTS

A. Ethical Principles and Regulations Governing the Protection of Human Subjects

i. Belmont Report

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established in 1974 with the passage of the National Research Act. The Commission met from 1974 to 1978 and published The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, on April 18, 1979. The Belmont Report identifies the basic ethical principles underlying the acceptable conduct of research involving human subjects. Those principles, respect for persons, beneficence, and justice, are now accepted as the three fundamental requirements for the ethical conduct of human subjects research and serve as the basis for regulations and guidelines pertaining to the protection of human subjects. The Institution's investigators, research staff, IRB members, IRB staff, and in working with sponsors, follow the ethical principles of the Belmont Report for all human subjects research.

a. **Autonomy and Respect** for persons involves recognition of the personal dignity and autonomy of individuals and necessitates special protection for persons with diminished autonomy. The ethical principle of respect for persons requires that researchers disclose complete information about the nature of research to prospective subjects and obtain their informed consent prior to engaging them in research-related activities. In addition, it justifies additional protections for individuals who are vulnerable or of diminished capacity.

b. **Beneficence** necessitates the protection of persons from harm by maximizing anticipated benefits and minimizing possible risks of harm. It is in consideration of this ethical principle that the IRB is required to conduct a systematic assessment of risks and benefits associated with research. Adhering to the ethical principle of beneficence, the IRB may review the scientific merits of a research study to determine that the potential benefits and the likelihood of their occurrence outweigh the potential risks and the likelihood of their occurrence.

c. **Justice** requires that the benefits and burdens of research be distributed fairly among individuals and different classes of people. Accordingly, this principle directs the IRB to carefully consider the selection of research subjects. The IRB must judge whether some classes are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Furthermore, the principle of justice requires that researchers apply equal selection standards to all potential subjects. Accordingly, they should not offer potentially beneficial research only to individuals who will make the most convenient and manageable subjects; likewise, they should not limit the subject population to certain groups - such as racial minorities, the socio-economically disadvantaged, the very sick, or the institutionalized, when conducting risky research.

The Belmont Report also provides important guidance related to distinguishing medical practice from research. The Report defines the term 'practice' as "interventions that are designed solely to enhance the well-being of an individual patient or client and that

have a reasonable expectation of success." The term 'research,' on the other hand, refers to "an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge." The Belmont Report explains that it is important for the distinction between practice and research to be clear to human subjects, particularly those who participate in research activities with the expectation of receiving some treatment for their illness or condition. The Belmont Report holds that this distinction is especially crucial in cases where a subject's treating physician is also the researcher. In such a context, the subject may harbor a "therapeutic misconception," believing that participation in the research must be the best option simply because the treating physician recommends it.

ii. DHHS Regulations (Title 45 Code of Federal Regulations)

The Institution holds a federal-wide assurance from OHRP and functions in full compliance with the applicable federal, state, and local laws. The DHHS regulations for the protection of human subjects in research were codified at the Code of Federal Regulations (CFR) Title 45 Part 46 (45 CFR 46) All research involving human subjects, which receives federal funding, must comply with the DHHS regulations OHRP is the federal oversight entity within DHHS responsible for the administration of 45 CFR 46.

The DHHS regulations contain four Subparts that provide the foundation for the review and approval of all research conducted at the Institution regardless of funding.

a. Subpart A, Federal Policy for the Protection of Human Subjects (Basic DHHS Policy for Protection of Human Research Subjects), has been adopted by seventeen federal agencies that conduct, support, or otherwise regulate human subjects research in order to ensure uniformity of the human subjects protection system. Subpart A is also referred to as the "Common Rule."

b. Subpart B of 45 CFR 46 regulates research involving pregnant women, human fetuses, and neonates.

c. Subpart C of 45 CFR 46 outlines additional protections for prisoners involved as subjects in research.

d. Subpart D of 45 CFR 46 describes additional regulations for children involved as subjects in research.

All research involving human subjects that is conducted by staff of the Institution on its premises or under its sponsorship, regardless of funding source, must be reviewed and approved by the IRB. This also applies to personnel who conduct research at other hospitals, institutions, or places external to the Institution. Individuals who are not affiliated with the Institution, but who are involved in research activities that involve the Institution's patients must also follow these policies and procedures.

iii. FDA Regulations (Title 21 Code of Federal Regulations)

The provisions of the Food, Drug, and Cosmetic Act of 1938 provide authority to the Food and Drug Administration (FDA) to regulate clinical investigations, development, and approval of drugs, biologics, and devices. The FDA regulations for the protection of human subjects are contained in Title 21 of the Code of Federal Regulations Part 50 (21 CFR 50). The FDA regulations governing IRBs are contained in Title 21 of the

Code of Federal Regulations Part 56 (21 CFR 56). All research activities involving food, investigational new drugs, biologics, or medical devices, and approved drugs, biologics, or medical devices which are used off-label must comply with all applicable FDA regulations and Good Clinical Practice (GCP) standards for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials.

The Institution participates in clinical research that is under the jurisdiction of the FDA, and complies with the regulations under 21 CFR 50, (Informed Consent); 21 CFR 50 Subpart D, 21 (Children); 21 CFR 56 (IRB Regulations); 21 CFR 312 (Investigational New Drug Applications); 21 CFR 612, (Biological Products); and 21 CFR 812 (Investigational Device Exemptions).

B. Definitions and Jurisdiction of the IRB

The Institution defines human subject research as any activity that either represents research that involves human subjects as defined by OHRP regulations, or any activity that represents research/clinical investigation that involves human subjects as defined by FDA regulations.

At the Institution, all research involving human subjects must comply with institutional policies and applicable regulations. Additionally, the Institution complies with all applicable state laws and regulations regarding human subjects' research. State law and regulations will supersede federal regulations when it imposes greater restrictions on research conduct (e.g., age of assent, age of consent, and surrogate decision-making, etc.). The Institution uses the following definitions from OHRP to determine what constitutes human subjects research. The proposal must involve both research and human subjects (as defined below) in order to be considered human subjects research.

Activities that meet the definition of human subjects research below are subject to review by the IRB. Included in the purview of the IRB is the review of all uses of human tissue/specimens, including autopsy material, as the IRB serves as the Privacy Board for research activities for the Institution.

i. Research

Both OHRP and the FDA define research as a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. OHRP has deemed the following activities not to be research [45 CFR 46.102(l)]:

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

(2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health

importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

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

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

ii. Clinical Investigation (FDA)

Any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA or the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit [21 CFR 50.3(c)].

iii. Human Subject

FDA defines a human subject as an individual who is or becomes a subject in research, either as a recipient of the test article or as a control or an individual on whose specimen a device was used. A subject may be either a healthy human or a patient [21 CFR 50.3(e)].

OHRP defines human subject as a living individual about whom an investigator (whether professional or student) conducting research:

1) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies or analyzes the information or biospecimens; or
2) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

iv. Intervention (OHRP)

Intervention includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulation of the subject or the subject's environment that are performed for research purposes.

v. Interaction (OHRP)

Interaction includes communication or interpersonal contact between an investigator and subject.

vi. Test Article (FDA)

Refers to any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to FDA regulation [21 CFR 50.3(c) and 21 CFR 50.3(j)].

vii. Private Information (OHRP)

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 that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

viii. Identifiable Private Information

Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

ix. Identifiable Biospecimen

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

x. Clinical Trial

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

C. Determining Whether an Activity Constitutes Human Subjects Research

The OHRP and FDA guidelines are used to determine if an activity is human subject research by applying the definitions outlined above.

i. Activities Subject to IRB Review

The Office of Research Integrity and Compliance (ORIC) offers guidance and direction on activities that may require IRB review. An activity requires IRB approval or determination of exempt status if the following criteria are met:

a. The proposed activity meets the definition of "research;"

b. The proposed activity will involve the collection of data or biospecimens from or about "human subjects;" and

c. Institutional involvement in the activity meets the criteria of "engagement" in research per OHRP guidance.

During consideration of inquiries regarding what may require IRB review, investigators are encouraged to contact ORIC staff for guidance. If required, investigators will be requested to submit an initial application via the electronic IRB system, with additional details regarding the proposed project for official determination.

Determinations may be made by the staff of ORIC following the regulatory definitions of "research" and "human subject" in addition to the OHRP letter on engagement of institutions in research. If necessary, an IRB Chair or Vice-Chair will participate in the review. In some cases, where the request is more involved, it may become necessary to consult further with federal oversight agencies. Final determinations will be communicated to the requestor via the electronic IRB systemIRB.

D. Research Collaborations and Engagement

The IRB is responsible for the oversight of all research involving human subjects (as defined by the regulations) that is conducted by members of the Institution's workforce, which includes medical staff, research staff, or employees regardless of the location of the research or funding source. The Institution's workforce is defined as those individuals who receive their paycheck from the Institution or one of its entities. Outside locations may need to apply for an assurance of compliance with OHRP if the location is engaged in the research and there is no IRB available at the site.

The IRB follows the definition of "collaboration" employed by NIH Office of Human Research Subjects, which states that collaboration exists if a researcher expects "something in return" as a result of having participated in a research activity. Collaborative activities may include the collection of specimens, visits to institutions to perform research activities or clinical work, exchange of information containing personal identifiers, preliminary data collection activities involving human subjects, substantive intellectual contributions to research techniques, protocol design, or interpretation of data, and under some circumstances, supplying important reagents, performing tests or analyzing data.

Before agreeing to participate in a research activity with an outside investigator, each Institutional investigator must first define the nature of the outside investigator's role and determine whether their participation will constitute "engagement" in human subjects research. If the outside investigator is engaged in human subjects research (as outlined in the OHRP Guidance on Engagement of Institutions in Human Subjects Research), IRB approval (or certification of exemption from IRB review) from the "home" institution of the outside investigator must be obtained before the outside investigator may engage in any study activity. If an outside investigator will be engaged in research activity at our Institution, they must also be added to the study personnel list. Common collaborative activities that would require IRB approval (or certification of exemption from IRB review) include:

i. The institution receives an award through a grant, contract, or cooperative agreement directly from HHS for the non-exempt human subjects research (i.e. awardee institutions), even where all activities involving human subjects are carried out by employees or agents of another institution.

ii. The institution's employees or agents intervene for research purposes with any human subjects of the research by performing invasive or noninvasive procedures.

iii. The institution's employees or agents intervene for research purposes with any human subject of the research by manipulating the environment.

iv. The institution's employees or agents interact for research purposes with any human subject of the research.

v. The institution's employees or agents obtain the informed consent of human subjects for the research.

vi. The institution's employees or agents obtain for research purposes identifiable private information or identifiable biological specimens from any source for the research. It is important to note that, in general, institutions whose employees or agents obtain identifiable private information or identifiable specimens for non-exempt human subjects' research are considered engaged in the research, even if the institution's employees or agents do not directly interact or intervene with human subjects. In

general, obtaining identifiable private information or identifiable specimens includes, but is not limited to:

a. observing or recording private behavior;

b. using, studying, or analyzing for research purposes identifiable private information or identifiable specimens provided by another institution; and

c. using, studying, or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the investigators.

In general, OHRP considers private information or specimens to be individually identifiable as defined in 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

E. Research Projects in which an Employee of Our Institution is a Consultant

The Institution's IRB review is required for any human subject research activity undertaken by an employee or agent of the Institution unless the employee or agent functions strictly as a consultant to the research team, holds no rights to the work (such as study design, data analysis, publication, co-authorship, etc.), and does not obtain, receive, or possess identifiable and private information about any research subject.

F. Investigator's Engaged in Research Conducted at Non-Institutional Sites

When an Institutional employee or agent participates in a multicenter study, or a research project by conducting research-related procedures at non-Institution site, the project must be reviewed and approved by both the Institution's IRB and the lead site's IRB or the local IRB of the research site. Documentation of the lead site's or local IRB approval for the conduct of research at the non-affiliated site must be maintained by the investigator.

More frequently, one IRB may opt to rely on the review of an external IRB. In this case, a Reliance Agreement, a formal written document that provides a mechanism for an institution engaged in research to delegate IRB review to an external IRB, is needed. Such an agreement may also be referred to as a Cooperative Agreement or IRB Authorization Agreement (IAA), is. Cooperative research projects are those projects covered by this policy that involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects. Agreements may cover reliance for a single study, categories of studies, or all human subjects research under an organization's Federalwide Assurance (FWA). Such an agreement should clearly identify the IRB of record and the delineation of responsibilities of all parties to facilitate collaboration and trust. While permissible under 45 CFR 46.114 for an institution to rely on an IRB of another OHRP-approved institution for protocol review, the Institution's IRB will ultimately determine whether it is in the best interests of the subjects to accept a determination by another IRB.

Under 21 CFR 56.114, institutions participating in multicenter studies may use joint review, rely on the review of another qualified IRB, or establish other arrangements to reduce duplicative efforts. For select multicenter trials, the Institution may choose to rely primarily on the review of a central or external IRB. If this is done, the Institution's IRB will review the multicenter protocol and supporting documents, the meeting minutes from the central or external IRB, and ensure the informed consent documents meet the Institution's requirements.

The IRB Chair and Institutional Official (IO) are consulted when ORIC receives requests for this type of arrangement. Investigators should contact the ORIC for questions regarding reliance agreements.

G. Quality Assurance and Quality Improvement Activities

It is important to recognize that some Quality Assurance (QA) or Quality Improvement (QI) activities conducted at the Institution may be classified as human subject research. Most QA and QI activities are assessments developed and initiated with the intent of assuring or improving the process, outcome, and/or efficiency of complex systems of health care. However, if the primary goal is to produce generalizable knowledge as defined in section B above, the activities are subject to the regulations governing the protection of human research subjects and require prior IRB review. Further guidance about requirements for QA/QI projects can be found in Section 7 Guidance on Quality Improvement and Assurance Projects of this manual. Investigators are also encouraged to contact ORIC staff for assistance in this area.

1.3 HUMAN RESEARCH PROTECTION PROGRAM (HRPP)

The Institution's Human Research Protection Program (HRPP) includes all persons and departments of the Institution engaged in the planning, design, review, conduct, or administrative support of any research involving human subjects. The Institution's HRPP is guided by the ethical principles outlined in this policy and is committed to the education of the research community and outreach to collaborating institutions.

A. HRPP Quality Improvement:

The Institution will routinely evaluate the resources needed for the HRPP, including but not limited to:

- Space
- Personnel
- IRB membership, education and training, and submission metrics
- Legal counsel
- Financial conflict of interest review and management
- HRPP routine monitoring and auditing programs (e.g. Post-Approval Monitoring Program)
- HRPP educational, training, and outreach programs

i. IRB Membership, Training, and Submission Metrics Quality Improvement Activities

- Review of IRB Membership

  ORIC will routinely evaluate IRB membership and qualifications to ensure that composition is in compliance with federal regulations. IRB Metrics

  ORIC tracks key IRB metrics (i.e., time from complete submission to approval for new studies submitted for all review types) and evaluates for ongoing process improvement. The HRPP is committed to maintaining IRB approval times to be in the top 50th percentile as compared to the Association for the Accreditation of Human Research Protection Programs (AAHRPP) annual HRPP metric reports. If approval times are lagging, investigation into causes will be initiated by ORIC administration and solutions to address delays will be designed and implemented.