Office of Human Research Ethics/IRB
Standard Operating Procedures

Effective September 9, 2019
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**Office of Human Research Ethics/IRB Standard Operating Procedures**

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Purpose

The University of North Carolina at Chapel Hill (UNC-Chapel Hill) fosters a research environment that promotes the respect for the rights and welfare of individuals recruited for, or participating in, research conducted by or under the auspices of the Organization. The review and conduct of research, actions by the Organization will be guided by the principles (i.e., respect for persons, beneficence, and justice) set forth in the Ethical Principles and Guidelines for the Protection of Human Subjects of Research (referred to as the Belmont Report). The actions of Organization will also conform to all applicable federal, state, and local laws and regulations. In order to fulfill this policy, the Organization has established a Human Research Protection Program (HRPP). The UNC-Chapel Hill HRPP, in partnership with its research community, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under its auspices. The research may be externally funded, funded from internal sources, or conducted without direct funding. The UNC-Chapel Hill HRPP is administered by the Office of Human Research Ethics (OHRE)

UNC Chapel Hill HRPP

2.1 HRPP Mission

The mission of the HRPP is to:

- Safeguard and promote the health and welfare of human research subjects by ensuring that their rights, safety and well-being are protected;
- Provide guidance and support to the research community in the conduct of research with human subjects;
- Assist the research community in ensuring compliance with relevant regulations;
- To provide timely and high quality education, review and monitoring of human research projects; and
- To facilitate excellence in human subjects research.

The HRPP includes mechanisms to:

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

2.2 Organizational Authority

The UNC-Chapel Hill Human Research Protection Program operates under the authority of the Organization policy “Human Research Protection Program (HRPP)”. As stated in that policy, the operating procedures in this document “...serve as the governing procedures for the conduct and review of all human research conducted under the auspices of the UNC-Chapel Hill. The HRPP Policy and these operating procedures are made available to all UNC-Chapel Hill investigators and research staff and are posted on the OHRE website (http://research.unc.edu/offices/human-research-ethics/).

2.3 Ethical Principles

The UNC-Chapel Hill is committed to conducting research with the highest regard for the welfare of human subjects. With the exception of transnational research, where consideration of alternative ethical principles may apply (see SOP 2001.2), the UNC-Chapel Hill upholds and adheres to the principles of The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (1979). These principles are:

1) Respect for Persons, which involves obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.

2) Beneficence, which involves ensuring that possible benefits are maximized and possible risks are minimized to all human subjects.

3) Justice, which involves the equitable selection of subjects.

The UNC-Chapel Hill Human Research Protection Program (HRPP), in partnership with its research community, community including researchers and research staff, IRB members and chairs, IRB staff, the organizational official, employees and students, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under its auspices.

2.4 Regulatory Compliance

The HRPP is responsible for ensuring compliance with federal regulations, state law and organizational policies. All human subjects research at The UNC-Chapel Hill is conducted in accordance with the policy and regulations found in the Common Rule and 21 CFR 50 and 56. The actions of The UNC-Chapel Hill will also conform to all other applicable federal, state, and
local laws and regulations such as Department of Defense (DoD), Department of Education (DoE), EPA, Family Educational Rights and Privacy Act (FERPA). Research supported by the Department of Defense (DoD) is reviewed and conducted in compliance with part 219 of title 32 CFR, part 980 of title 10 USC, applicable parts of title 21 CFR (50, 56, 312, 600, 812), DoD Instruction 3216.02, DoD Directive 3210.07, and applicable additional requirements from respective DoD component(s).

Research involving the use of Protected Health Information is reviewed and conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA), 45 CFR Part 160, 162, and 164.

Research involving the use of student educational records is reviewed and conducted in accordance with the Family Educational Rights and Privacy Act (FERPA), 34 CFR Part 99.

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

The UNC-Chapel Hill voluntarily applies the International Conference on Harmonization (“ICH”) Good Clinical Practices (“GCP”) Guidelines (sometimes referred to as “ICH-GCP” or “E6”) to clinical research conducted under its IRB. In general, UNC-Chapel Hill applies the ICH-GCP guidelines only to the extent that they are compatible with FDA and DHHS regulations.

2.5 Federalwide Assurance (FWA)

The federal regulations require that federally-funded human subject research only be conducted at facilities covered by a Federalwide Assurance (FWA) approved by the DHHS Office for Human Research Protections (OHRP). An FWA is an organization’s assurance to the federal government that human subject research conducted at that site is in compliance with federal regulations pertaining to the protection of human subjects. The FWA designates the Institutional Review Board that will review and oversee the research, specifies the ethical principles under which the research will be conducted, and names the individuals who will be responsible for the proper conduct of the research.

The UNC-Chapel Hill has an OHRP-approved Federalwide Assurance (FWA00004801) and has designated 6 IRB(s) (registered as 538, 539, 1648, 1649, 540, 9770).

In its FWA, The UNC-Chapel Hill has opted to limit the application of the FWA to non-exempt human subject research conducted or supported by DHHS or federal agencies that have adopted the Common Rule.

2.6 Research Under the Auspices of the Organization

Research under the auspices of the organization includes research conducted at this organization, conducted by or under the direction of any employee or agent of this organization (including students) in connection with his or her organizational responsibilities, conducted by or under the direction of any employee or agent of this organization using any property or facility of this organization, or involving the use of this organization's non-public information to identify, contact, or study human subjects.
**Employee or Agent.** For the purposes of this document, employees or agents refers to individuals who: (1) act on behalf of the organization; (2) exercise organizational authority or responsibility; or (3) perform organizationally designated activities. “Employees and agents” can include staff and students, among others.

**Engagement.** The Department of Health and Human Services (DHHS) regulations [45 CFR 46.103[a]] require that an institution “engaged” in human subject research conducted or supported by a Federal Department or Agency provide the Office for Human Research Protection (OHRP) with a satisfactory assurance of compliance with the DHHS regulations, unless the research is exempt under 45 CFR 46.101(b). “In general, an institution is considered engaged in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research.” In general, institutions that receive an award through a grant, contract, or cooperative agreement directly from DHHS for the non-exempt human subjects research (i.e. awardee institutions), are also considered engaged in research even where all activities involving human subjects are carried out by employees or agents of another institution.

FDA regulations are oriented to the responsibilities of IRBs, investigators, and sponsors as opposed to institutions. In general, FDA-regulated research conducted in The UNC-Chapel Hill facilities or by The UNC-Chapel Hill Principal or Sub-Investigators (as defined on the FDA 1572 or delegation of responsibilities log) requires review by an UNC-Chapel Hill designated IRB. Exceptions to this requirement may be granted on a case-by-case basis (e.g., when The UNC-Chapel Hill’s involvement in the research is limited to the provision of a common diagnostic procedure and associated reading or analysis).

The IRB Compliance Manager with the assistance of the OHRE Director and staff as needed, will determine whether the UNC-Chapel Hill is engaged in a particular research study. Investigators and other institutions may not independently determine the UNC-Chapel Hill engagement.

When the UNC-Chapel Hill is engaged in research, the Institutional Official may choose to enter into an agreement to cede review to an external IRB. (See SOP 901 for details on ceding review.)


2.7 **Written policies and procedures**

The UNC-Chapel Hill Standard Operating Policies and Procedures for Human Research Protection detail the policies and regulations governing research with human subjects and the requirements for submitting research proposals for review by the UNC-Chapel Hill IRB. This is not a static document. The policies and procedures are annually reviewed and revised by the OHRE Director or his/her designee. The OHRE Director will approve all revisions of the policies and procedures.
The OHRE Director will keep the Organization research community apprised of new information that may affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues on its website and through campus electronic mailing lists. The policies and procedures will be available on the UNC-Chapel Hill IRB website and printed/electronic copies will be available upon request. Changes to the policies and procedures are communicated to investigators and research staff, and IRB members and IRB staff by way of the OHRE website, town hall meetings, email and other methods as appropriate.

2.8 The UNC-Chapel Hill HRPP Structure

The HRPP consists of various individuals and committees such as: the Institutional Official, the Director of the OHRE, the IRB Managers and staff, the IRB(s), the Institutional Biosafety Committee (e.g., for gene transfer research), Radiation Safety Committee, Radioactive Drug Research Committee, Conflict of Interest Committee, Office of Sponsored programs, Legal Counsel, investigators, research staff, health and safety staff (e.g., Biosafety Officer, Radiation Safety Officer) and research pharmacy staff. The objective of this system is to assist the organization in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

The following officials, administrative units and individuals have primary responsibilities for human subject protections:

2.8.1 Institutional Official

The ultimate responsibility of the HRPP resides with the Institutional Official (IO) of the program. The IO is legally authorized to represent the UNC-Chapel Hill. The IO is the signatory of the FWA and assumes the obligations of the FWA. At the UNC-Chapel Hill, the Vice Chancellor for Research is the Institutional Official. The IO is responsible for ensuring that the UNC-Chapel Hill HRPP and IRB(s) have the resources and support necessary to comply with all organizational policies, laws, and regulations that govern human subject research. Such resources include, but are not limited to:

- Staffing commensurate with the size and complexity of the research program;
- Appropriate office space, equipment, materials, and technology;
- Resources for the production, maintenance, and secure storage of HRPP and IRB records;
- Resources for auditing and other compliance activities and investigation of non-compliance;
- Access to legal counsel; and
- Supporting educational opportunities related to human research protections for IRB members, relevant administrative staff, and all members of the research team.
- Support for evaluation of Conflict of Interest; and
• Support for Community Outreach.

The IO conducts and documents an annual review of HRPP and IRB function, requirements, and resources and makes adjustments as needed.

The IO is also responsible for:

• Fostering, supporting and maintaining an organizational culture that supports the ethical conduct of all research involving human subjects and the adherence to regulations and organizational policies;

• Ensuring that the IRB functions independently by, among other mechanisms, being directly accessible to the IRB Chair(s) and members if they experience undue influence or if they have concerns about the function of the IRB;

• Oversight of the Institutional Review Board (IRB);

• Oversight over the conduct of research conducted by all UNC-Chapel Hill investigators;

• Assuring the IRB members are appropriately knowledgeable to review research in accordance with ethical standards and applicable regulations;

• Assuring that all investigators are appropriately knowledgeable to conduct research in accordance with ethical standards and applicable regulations; and

• Oversight of the development and implementation of an educational plan for IRB members, staff and investigators.

The IO must complete the OHRP Human Subject Assurance Training and any other appropriate training on human research protections. The OHRE Office will provide ongoing continuing education for the IO concerning human research protections.

The designated IO is made known to employees of the organization and is accessible by phone, email, in person or other methods of communication. The IRB Chairs and OHRE Director have access to the IO for any concerns or issues related to the HRPP.

In the performance of these duties, the IO has the authority to delegate such activities as may be necessary in order to effectively administer the program. However, the IO is ultimately responsible and is expected to be knowledgeable about all human subject protections responsibilities at the organization.

2.8.2 The Office of Human Research Ethics (OHRE)

The Office of Human Research Ethics (OHRE) is responsible for ethical and regulatory oversight of research at UNC-Chapel Hill that involves human subjects. The OHRE administers, supports, and guides the work of the Institutional Review Boards (IRBs) and all related activities.

2.8.3 Director of the OHRE

The Director of the OHRE is selected by and reports to the Institutional Official (IO) through the Associate Vice Chancellor for Research Compliance and is responsible for:
1. Developing, managing and evaluating policies and procedures that ensure compliance with all state, and federal regulations governing research. This includes monitoring changes in regulations and policies that relate to human research protection and overseeing the administration of the IRB.

2. Advising the IO on key matters regarding research at the UNC-Chapel Hill.

3. Implementing the organization’s HRPP policies and procedures.

4. Submitting, implementing and maintaining an approved FWA through the IO and the Department of Health and Human Services Office of Human Research Protection (OHRP).

5. Managing the finances of the UNC-Chapel Hill OHRE.

6. Assisting investigators in their efforts to carry out Organization’s research mission.

7. Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program.

8. Developing training requirements as required and as appropriate for investigators, subcommittee members and research staff, and ensuring that training is completed on a timely basis.

9. Serving as the primary contact at the UNC-Chapel Hill for the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services, the Food & Drug Administration (FDA) and other federal regulatory agencies.

10. Day-to-day responsibility for the operation of the HRPP office, including supervision of HRPP and IRB staff.

11. Responding to questions regarding the protection of human subjects.

12. Working closely with the Chairs of the IRBs on the development of policy and procedures, as well as organizing and documenting the review process.

2.8.4 OHRE Staff

In addition to the leadership structure described above, other support staff members for the OHRE and IRB include Compliance Manager, Education and Training Manager, QA/QI Manager, Data and Information Manager, IRB Senior Analysts, IRB Analysts, Business System Analysts, Office Manager, and Administrative Assistants. The OHRE and IRB staff for the UNC-Chapel Hill must comply with all ethical standards and practices. The duties and responsibilities for all staff are found in their respective job descriptions, and their performance is evaluated on an annual basis. The UNC-Chapel Hill OHRE staff reports to the OHRE Director, who has day-to-day responsibilities for its operations.

2.8.5 Institutional Review Board (IRB)

The UNC-Chapel Hill has six on-site IRBs, appointed by the Institutional Official (IO). The IRBs prospectively reviews and makes decisions concerning all human research conducted at the UNC-Chapel Hill facilities, by its employees or agents, or under its auspices unless another IRB
has been designated to do so. The IRB is responsible for the protection of rights and welfare of human research subjects at the UNC-Chapel Hill through review and oversight of safe and ethical research. It discharges this duty by complying with the requirements of federal and state regulations, the FWA, and organizational policies. (See SOP 401 for a detailed discussion of the UNC-Chapel Hill IRB and external IRBs.)

The IRB functions independently of, but in coordination with, other organizational committees and officials. The IRB, however, makes its independent determination whether to approve or disapprove a research plan based upon whether or not human subjects are adequately protected.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the organization. However, those officials may not approve human research that has not been approved or has been disapproved by the IRB.

2.8.6 Counsel’s Office

The UNC-Chapel Hill HRPP relies on the Office of University Counsel for the interpretations and applications of state law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research. Legal Counsel will also advise the IRB about other legal issues such as who is a child, and who can serve as a legally authorized representative or guardian. When there are any conflicts between federal or national law and other applicable laws, the Legal Counsel will determine the appropriate resolution.

2.8.7 Department Chairs and/or Organizational Leaders

Department Chairs and organizational leaders are responsible for ensuring that the investigator is qualified by training and experience to conduct the proposed research. For each research study submitted to the UNC-Chapel Hill IRB for approval, the department chair or leader must certify that s/he accepts responsibility for supporting adherence to the federal and state regulations and organizational policies governing the protection of human subjects of research, including applicable organizational credentialing requirements. Department chairs/leaders are responsible for assuring that investigators have the resources required to conduct the research in a way that will protect the right and welfare of participants. Such resources include but are not necessarily limited to personnel, space, equipment and time.

Department chairs/leaders are required to review all proposals before they are submitted to the IRB for review. The signature of the Department chair or leader indicates that (1) the investigator is qualified and has the necessary resources to safely conduct the study, and (2) attests to the scientific merit of this study, which means

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

The investigator is ultimately responsible for the protection of the human subjects who participate in research. The investigator is expected to abide by the highest ethical standards when developing a research plan that incorporates the principles of the Belmont Report. The investigator is expected to conduct research in accordance with the IRB approved research plan and to oversee all aspects of the research by providing training and supervision of support staff, including oversight of the informed consent process. All subjects must give informed consent unless the requirement has specifically been waived by the IRB. Investigators must establish and maintain an open line of communication with research subjects within their responsibility. In addition to complying with all applicable policies and standards of regulatory bodies, investigators must comply with organizational and administrative requirements for conducting research. The investigator is responsible for ensuring that all research staff complete all organizational required training as well as training for their responsibilities in any given specific research study. When investigational drugs or devices are used, the investigator is responsible for providing a plan for their storage, security, dispensing, accounting, and disposal.

2.8.9 Other Related Units

2.8.9.1 Office of Sponsored Research and Office of Industry Contracting

Office of Sponsored Research (OSR) and Office of Industry Contracting (OIC) staff review all research agreements with all sponsors including federal, foundation, and non-profit sponsors. This review ensures that all terms of the award (grant or contract) are in compliance with organizational policies. Only designated senior individuals within the Office of Sponsored Research and OIC have the authority to approve research proposals and to execute research agreements on behalf of the organization.

The OSR and OIC ensure that required AAHRPP language (see SOP 1601) is included in contracts. The Office of Sponsored Research and OIC have access to the IRB submission to confirm that the contract and the consent documents are consistent in terms of costs to subjects and who pays in case of injury. OSR, OIC and the IRB office coordinate efforts to ensure that all applicable individuals have filed appropriate COI disclosures to meet investigator COI policies.

When the grant or contract agreement includes human research activities that will be conducted by investigators who are not employees or agents of the UNC-Chapel Hill a subcontract is executed between the UNC-Chapel Hill and the collaborating institution. The subcontract includes the requirement for the collaborating institution to assure compliance with federal regulations for the protection of human subjects in research and to provide documentation of current and ongoing IRB approval. The collaborating institution must also ensure that key personnel involved in human subject research are in compliance with the NIH policy on education in the protection of human research subjects and provide documentation of education of key personnel to the UNC-Chapel Hill, when required.
2.8.9.2 UNC Hospitals Investigational Drug Services Pharmacy

A pharmacist from UNC Hospitals Pharmacy serves on the IRB, allowing the Pharmacy to have complete information about all IRB approved research that takes place at the UNC-Chapel Hill and under its jurisdiction. The Pharmacist member assures that information about all studies involving drugs used in research is shared with both the Pharmacy Staff as appropriate and that the UNC Hospitals Investigational Drug Services and the Pharmacy and Therapeutics Committee is made aware of IRB approved research involving drugs.

The UNC Hospitals Investigational Drug Services Pharmacy is responsible for storing, accounting for, dispensing, and compounding of most investigational drugs used in research, whether conducted inpatient or outpatients. The manufacture/compounding of drug products not commercially available is coordinated by the UNC Hospitals Investigational Drug Services Pharmacy. Waivers from use of the UNC Hospitals Investigational Drug Services Pharmacy for handling investigational drugs will be considered on a case by case basis by the UNC Hospitals Investigational Drug Services Pharmacy, with required information regarding storage, accounting, dispensing etc. provided within the IRB application.

The Pharmacy is available to provide guidance to investigators in relation to the management of the study drugs.

2.8.10 Relationship Among Components

The Research Compliance Steering Committee will meet to ensure a dialogue is maintained between the various compliance entities at the Organization. Membership is comprised of Directors and members from Office of Industry Contracting, Office of University Counsel, Office of Sponsored Research, Office of Human Research Ethics, Conflict of Interest, Office of Clinical Trials, Environmental Health and Safety, Institutional Animal Care and Use Committee, HIPAA Office, Office of Technical Commercialization, and UNC Hospitals Compliance and Research Integrity with the Associate Vice President for Research Compliance as chair. The committee will act in an advisory capacity to the Vice President for Research, monitoring the effectiveness of existing compliance programs, developing new or revised policies as changes in requirements occur, and disseminating updated compliance information to the research community.

2.8.10.1 Study-Specific Coordination

In addition to IRB approval, the Investigator must obtain and document the approval, support, or permission of other individuals and departments or entities impacted by the research as well as approval by other oversight committees, including, but not limited to:

- Pathology
- University Hospital/Affiliated Hospital/s
- Pharmacy
- Radiology/Imaging
- Nuclear Medicine
• Nursing
• Confirmation that permission to enter classrooms or hospital units will be obtained
• Confirmation that permission from external research locations (sites) will be obtained
• Departmental approvals
• Database access permissions (e.g., Medical/Educational Records)
• Institutional Biosafety Committee
• Radiation Safety Committee
• Radioactive Drug Research Committee
• Conflict of Interest Committee
• Scientific/Scholarly Review Committee

For any that are indicated, a letter of support, collaboration, permission, or approval from the designated authority, should be included in the Initial Study Application to the IRB. The application will be reviewed in the IRB Office to ensure that all necessary letters are included. Final IRB approval will not be given until all necessary letters are received. The IRB may request review or consultation with any of the above listed or other organizational committees or components even when such review or consultation is not technically required by policy.

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

3 Definitions

Common Rule. The Common Rule refers to the “Federal Policy for the Protection of Human Subjects” adopted by a number of federal agencies. Although the Common Rule is codified by each agency separately, the text is identical to DHHS regulations in 45 CFR 46 Subpart A. For the purposes of this document, references to the Common Rule will cite the DHHS regulations.

Human Subject Research. Human Subject Research means any activity that meets the definition of “research” and involves “human subjects” as defined by either the Common Rule or FDA regulations.

Note: The terms “subject” and “participant” are used interchangeably in this document and have the same definition.

Research. The Common Rule defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research 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.
For the purposes of this policy, a “systematic investigation” is an activity that involves a prospective study plan that incorporates data collection, either quantitative or qualitative, and data analysis to answer a study question. Investigations designed to develop or contribute to generalizable knowledge are those designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.

The FDA has defined “research” as being synonymous with the term “clinical investigation.” A clinical investigation, as defined by FDA regulations, means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [21 CFR 50.3(c), 21 CFR 56.102(c)]

Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act means any use of a drug other than the use of an approved drug in the course of medical practice. [21 CFR 312.3(b)]

Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act means any activity that evaluates the safety or effectiveness of a device. [21 CFR 812.2(a)]

Any activity in which results are being submitted to or held for inspection by FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research. [21 CFR 50.3(c), 21 CFR 56.102(c)]

**Human Subject.** A human subject as defined by the Common Rule is a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or through identifiable private information [45 CFR 46.102(f)].

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

- Interaction means communication or interpersonal contact between investigator and subject.

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

For research covered by FDA regulations, human subject means an individual who is or becomes a participant in a clinical investigation, either as a recipient of the test article or as a control. A subject may be in normal health or may have a medical condition or disease. In the case of a medical device, a human subject also includes any individual on whose specimen an investigational device is used or tested or used as a control. When medical device research involves in vitro diagnostics and unidentified tissue specimens, the FDA defines the unidentified tissue specimens as human subjects.

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

Test articles covered under the FDA regulations include, but are not limited to:

a) **Human drugs** – The primary intended use of the product is achieved through chemical action or by being metabolized by the body. A drug is defined as a substance recognized by an official pharmacopoeia or formulary; a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; a substance (other than food) intended to affect the structure or any function of the body; a substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.)
http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm

b) **Medical Devices** - A device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm

c) **Biological Products** - include a wide range of products such as vaccines, blood and blood components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and
tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.
http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm
d) **Food Additives** - A food additive is defined in Section 201(s) of the FD&C Act as any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use); if such substance is not Generally Recognized As Safe (GRAS) or sanctioned prior to 1958 or otherwise excluded from the definition of food additives.
http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm
e) **Color Additives** - A color additive is any dye, pigment or substance which when added or applied to a food, drug or cosmetic, or to the human body, is capable (alone or through reactions with other substances) of imparting color. Color additives for use in food, drugs, and cosmetics require premarket approval. Color additives for use in or on a medical device are subject to premarket approval, if the color additive comes in direct contact with the body for a significant period of time.
http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm
f) **Foods** - Foods include dietary supplements that bear a nutrient content claim or a health claim.
g) **Infant Formulas** – Infant formulas are liquid foods intended for infants which substitute for mother’s milk.
h) **Electronic Products** - The FDA regulates certain classes of electronic products including radiation-emitting electronic products such as microwaves and x-rays.

**Institutional Review Board (IRB)** - An IRB is a board designated by UNC-Chapel Hill to review, approve the initiation of, and conduct periodic review of research involving human participants, as defined above. The primary purpose of such review is to assure the protection of the rights and welfare of the human participants. The IRB may be assigned other review functions as deemed appropriate by UNC-Chapel Hill.
REFERENCES

4.1 DHHS Regulations: 45 CFR 46
4.2 FDA Regulations: 21 CFR 50 and 56.
4.3 DoD Instruction 3216.02, DoD Directive 3210.07
4.4 Health Insurance Portability and Accountability Act (HIPAA), 45 CFR Part 160, 162, and 164.
4.5 Family Educational Rights and Privacy Act (FERPA), 34 CFR Part
1 Purpose

The University of North Carolina at Chapel Hill (UNC-Chapel Hill) performs Quality Assurance and Improvement activities for the purposes of monitoring the safety of ongoing studies and measuring and improving human research protection effectiveness, quality, and compliance with organizational policies and procedures and applicable federal, state, and local laws.

2 Procedures

2.1 External Monitoring, Audit, and Inspection Reports

All reports from external monitors, auditors, or inspectors must be submitted by investigators. The Office of Clinical Trials Clinical Trials Quality Assurance (CTQA) Program is responsible for reviewing such reports in order to monitor for issues that could impact the rights or welfare of human subjects and for issues indicative of possible serious or continuing non-compliance. If such issues are identified, the researcher will be instructed to submit a “new safety information” report to the IRB. Such reports will be handled as described in Section (See SOPs 1401 & 1402).

2.2 Investigator Compliance Reviews

The OHRE Quality Assurance/Quality Improvement (QA/QI) Manager is responsible for conducting post-approval Directed (“for cause”) audits and periodic (not “for cause”) reviews of the consent process. Additionally, the IRB may appoint a subcommittee for the purpose of conducting a for-cause or not for-cause compliance review of one or more research plans under its jurisdiction. The subcommittee may be composed of IRB members and staff from within, or individuals from and outside of the organization. The Clinical Trials Quality Assurance (CTQA) Program conducts random (non-directed) post-approval reviews for a percentage of clinical research studies as well as “friendly” audits (at the request of the research team).

Compliance reviews are conducted to assess investigator compliance with federal, state, and local law, and the UNC-Chapel Hill policies, and to identify areas for improvement, and to provide recommendations based on existing policies and procedures. The results of directed compliance reviews will be reported to the OHRE Director, the IRB, and the investigator. Any non-compliance will be handled according to the procedures in SOP 1402.
If it is identified that subjects in a research project have been exposed to unexpected serious harm, the reviewer will promptly report such findings to the Safety Committee Chair and/or Compliance Manager for immediate action. IRB Chairs have authority to temporarily suspend research in cases where subjects may be exposed to harm.

If issues are identified that indicate possible misconduct in research, the procedures in the Policy and Procedures on Responding to Allegations of Research Misconduct (http://policies.unc.edu/files/2014/10/Research-Misconduct.pdf) will be initiated.

Compliance reviews may include:

a) Requesting progress reports from investigators;
b) Examining investigator-held research records;
c) Contacting research subjects;
d) Observing research sites where research involving human research subjects and/or the informed consent process is being conducted;
e) Reviewing advertisements and other recruiting materials;
f) Reviewing projects to verify from sources other than the investigator that no unapproved changes have occurred since previous review;
g) Assuring that the consent documents include the appropriate information and disclosures about conflicts of interest;
h) Monitoring HIPAA authorizations;
i) Conducting other monitoring or auditing activities as deemed appropriate by the HRPP or IRB.

2.3 IRB Compliance Reviews

The OHRE QA/QI Manager with, or without, the assistance of an outside organization, will periodically review the activities of the IRB to assess compliance with regulatory requirements and to identify areas for improvement; this will include a review of IRB records at least annually. Review activities may include:

a) Review of the IRB minutes to determine that adequate documentation of the meeting discussion has occurred. This review will include assessing the documentation surrounding the discussion for protections of vulnerable populations as well as risk/benefit ratio and consent issues that are included in the criteria for approval;
b) Review of the IRB minutes to assure that quorum was met and maintained;
c) Review of IRB documentation, including IRB minutes, to assess whether privacy provisions, according to HIPAA, have been adequately reviewed, discussed and documented;
d) Evaluating the continuing review discussions to assure they are substantive and meaningful and that no lapse has occurred since the previous IRB review;
e) Reviewing IRB files to assure retention of appropriate documentation and consistent organization of the IRB file according to current policies and procedures;
f) Reviewing the IRB database to assure all required fields are completed accurately;
j) Verifying IRB approvals for collaborating institutions or external performance sites;
k) Reviewing the appropriate metrics (for example, time from submission to first review) to evaluate the quality, efficiency, and effectiveness of the IRB review process;
l) Reviewing the workload of IRB staff to evaluate appropriate staffing level; and
m) Other monitoring or auditing activities deemed appropriate.

The OHRE Director will review the results of IRB QA/QI reviews. If any deficiencies are noted in the review, a corrective action plan will be developed by the Director, QA/QI Manager, and as applicable, IRB Chairs and/or staff. The Director (or designee) will have responsibility for implementing the corrective action plan, and for evaluating the results.

2.4 HRPP Quality Assessment and Improvement

At least annually, the Director, in collaboration with members of the OHRE executive committee, will define Quality Improvement goals for the year. The targeted issues, goals, and means to measure progress are documented in a written QA/QI plan. In order to evaluate whether the defined goals are being achieved, the QA/QI manager in collaboration with the Data Information Manager/Business Systems Analyst, collects, records, and provides a written report to the Director. At minimum, the report will contain:

- The goals of the quality assessment/improvement plan with respect to measuring effectiveness, identifying opportunities for improvement and achieving and maintaining targeted levels of quality, efficiency, effectiveness and compliance are stated
- At least one objective to achieve or maintain compliance is defined
- At least one measure of compliance is defined
- The methods to assess compliance and make improvements are described
- At least one objective of quality, efficiency, or effectiveness is defined
- At least one measure of quality, efficiency, or effectiveness is defined
- The methods to assess quality, efficiency, or effectiveness and make improvements are described

Results are reviewed by the OHRE Director in order to identify trends and to determine if systemic changes are required to prevent re-occurrence. If so, the Director and members of the OHRE executive committee will collaborate in the development of a corrective action plan, its implementation, and evaluation of its effectiveness.
The Data Information Manager/Business Systems Analyst is responsible for tracking internal metrics that are informative in considering IRB and Investigator efficiency such as the amount of time from receipt of a submission through pre-review, assignment to the IRB, and final approval and the amount of time it takes investigators to develop and submit responses to pre-review and IRB requirements. Metrics reports will be provided to the Director as requested.
1 Purpose

Recognizing that a vital component of a comprehensive human research protection program is an education program for all individuals involved with research subjects, the University of North Carolina at Chapel Hill (UNC-Chapel Hill) is committed to providing training and an on-going educational process for IRB members, the staff of the IRB and HRPP Office, investigators and members of their research team, related to ethical concerns and regulatory and organizational requirements for the protection of human subjects.

2 Procedures

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

2.1.1 Orientation

New IRB members, including alternate members will meet with the Education & Training Manager of the HRPP Office for an informal orientation session when they observe their first IRB meeting. Prior to this orientation meeting, new members are sent a set of 6 PowerPoint Modules that provide an overview of IRB function, ethics, regulations, HIPAA, IRB 111 Review Criteria and operations. New members are also required to complete the PRIM&R on-line course for IRB Members (eROC), or other equivalent, approved research training prior to becoming a voting member. At the orientation session, new members also have a training session with the Data & Information Manager on the electronic IRB program. At orientation the new member will be given an IRB Handbook, Amdur & Bankert, 3rd Edition and an encrypted flash drive that includes:

- Belmont Report;
- Nuremberg Code
- Helsinki Declaration
- TriCouncil Ethical Conduct
- 2002 CIOMS International Ethical
- 2011WHO Standards & Operational Guide
- E6 Guideline
- OHRP 2016 International Compilation of Human Research Standards
• OHRP Informed Consent Checklist
• Past IRB Meeting Educational Presentations
• 1963 Milgram Behavioral Study
• 1966 Beecher “Ethics & Clinical Research”
• 1972 Heller Syphilis Victims
• 1986 Krugman Willowbrook
• 1966 Faden Advisory Committee
• 2001 Gelsinger, “Jesse’s Intent”
• 2010 Physicians Experiments in Torture
• 2011 Reverby Normal Exposure
• Consent templates
• Social Security Number Disclosure, use for research and use as an identifier
• The UNC-Chapel Hill Policies and Procedures for the Protection of Human Subjects;
• Federal regulations relevant to the IRB; and
• Tools used by IRB reviewers (checklists etc.).

New members are required to complete the Initial Education requirement for IRB members before they may serve as Primary Reviewer.

2.1.2 Initial CITI Education

IRB members and HRPP and IRB administrators and staff will complete the required modules in the CITI Course in the Protection of Human Research Subjects. The modules are grouped by categories of research. Researchers, IRB Members & Staff are only required to complete one group of modules that best fits the type of research they normally conduct.

• **Group 1**: Biomedical Research: Medical, physiological or pharmacological studies that typically involve direct contact with subjects. Includes, but is not limited to, research with drugs, devices or other interventions.

• **Group 2**: Social and Behavioral Research: Studies on sociological, psychological, anthropological or educational phenomena that typically involve direct contact with subjects. Does not include drug or device studies.

• **Group 3**: Data and Specimens ONLY: No direct contact with human subjects. Research limited to use of records, data (including secondary data sets), or biological samples.
2.1.3 Continuing Education for IRB Members

To ensure that oversight of human research is ethically grounded and the decisions made by the IRB is consistent with current regulatory and policy requirements, training is continuous for IRB members throughout their service on the IRB.

In addition to initial training requirements, IRB members and HRPP and IRB administrators and staff must also satisfy continuing education requirements on an annual basis. The UNC-Chapel Hill uses the following activities as a means for offering continuing education to IRB members and HRPP and IRB administrators and staff:

- Annual IRB Member Retreat
- IRB Meeting 10-minute educational presentations which are mailed to every IRB Member and senior staff each month and are also posted on a members’ webpage
- Monthly email to all IRB Members & Analysts of the meeting in-service materials and additional regulatory updates, recent publications and guidance.
- A Member & Staff website that includes copies of education handouts, dates of upcoming educational offerings of interest to members & staff; links to other training resources; references from governmental sites (OHRP, FDA, NIH, DOE, EPA); educational offerings from OHRP and other IRBs; a membership directory; a link to CITI; AAHRPP and topical informational sites (FDA Drugs; Medline Plus tutorials; Certificates of Confidentiality).
- Periodic webinar offerings
- Monthly sessions with the IRB Analysts
- Monthly sessions with IRB non-scientist and unaffiliated members
- Identification and dissemination by the Director of new information that might affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues to IRB members via email, mail, or during IRB meetings; and
- Unlimited access to the IRB Office resource library.

The activities for continuing education vary on a yearly basis depending on operating budget and areas of need, as determined by the Education & Training Manager in consultation with the OHRE Director. The Education & Training Manager tracks whether each individual has satisfied the requirements. IRB members who have not fulfilled their continuing education requirements will not be assigned as primary or secondary reviewer until they are fulfilled. Continuing failure to complete training may result in the individual being removed or not renewed as an IRB member. Fulfillment of training requirements is included as part of the evaluation of the performance of IRB members/alternates. The Institutional Official (IO) will provide support to send as many members of the IRB as possible to attend the annual PRIM&R conference or regional OHRP conferences on human research protections.
2.2  Training / Ongoing Education of Investigators and Research Team

As stated previously, a vital component of a comprehensive human research protection program is an education program for all individuals involved with research subjects. The UNC-Chapel Hill committed to providing training and an on-going educational process for investigators and members of their research team related to ethical concerns and regulatory and organizational requirements for the protection of human subjects.

2.2.1  Initial Education

Investigators, key personnel, and other members of the research team must complete the UNC-Chapel Hill required core modules in the CITI Course in the Protection of Human Research Subjects including the module on Conflicts of Interest. Evidence of training for each member of the research team must be documented for every new research study application and application for continuing review.

New research plans and applications for continuing review will not be approved from investigators who have not completed the initial education requirement.

While research plans and applications for continuing review will be accepted and reviewed if the investigator holds a current certification of training, final approval will not be granted until all co-investigators and members of the research team have completed the initial education requirement.

2.2.1.1  Documentation of Equivalent Education

If individuals can provide documentation verifying that they have successfully completed human subject research training equivalent to that required by the UNC-Chapel Hill they may request a substitution of the requirement for Initial Education. The OHRE Director or designee will review the documentation and determine if it satisfies organizational standards.

2.2.1.2  Continuing Research Ethics Education Requirements

Continuing education requirements in the Protection of Human Research Subjects (as described above) must be completed at least every 3 years. Continuing education is tracked by the electronic IRB system. Final approval of initial and continuing review will not be granted until all appropriate members of the research team have completed the designated CITI refresher course.

2.2.2  Additional Educational Opportunities

The Education & Training Manager and other IRB Staff make a number of presentations throughout the UNC CH campus. These presentations include:

- Requests from study teams for additional training,
- Requests for class presentations on IRB Overview as part of an undergraduate or graduate level class,
- Requests to lead research ethics seminars for residents,
• Twice a year an IRB Overview is presented by IRB staff in the orientation series of lectures for new study coordinators.
1 Purpose

The University of North Carolina at Chapel Hill (UNC-Chapel Hill) has established an Institutional Review Board (IRB) to ensure the protection of human subjects in research conducted under the auspices of the UNC-Chapel Hill.

All non-exempt human subject research conducted under the auspices of the UNC-Chapel Hill must be reviewed and approved by the UNC-Chapel Hill IRB or another designated IRB prior to the initiation of the research unless it has been determined that the UNC-Chapel Hill is not engaged in the research (See SOP 101.2.6).

2 UNC-Chapel Hill IRBs

Although the UNC-Chapel Hill has authorized a number of IRBs to fulfill the review and oversight function, all on-site IRBs follow the same policies and procedures. Therefore, for the purposes of this document, all on-site IRBs will be referred to as the UNC-Chapel Hill IRB.

UNC-Chapel Hill has six on-site IRBs.

The UNC-Chapel Hill also uses the services of 5 off-site IRBs. They are:

- Commercial IRBs (WIRB-Copernicus Group, Sterling, and Advarra): for all industry sponsored, multi-site clinical trials unless given permission otherwise by the OHRE Director or Reliance/Compliance Leadership to utilize the UNC-Chapel Hill IRB.
- NCI’s Adult CIRB: for applicable cooperative oncology group protocols/studies involving adult subjects
- NCI’s Pediatric CIRB: for applicable cooperative oncology group protocols/studies involving minor subjects
The authorized off-site IRBs that serve as the IRB-of-record for the UNC-Chapel Hill have the same authority as the on-site IRBs and all determinations and findings of the off-site IRBs are equally binding on all research under the auspices of the organization.

2.1 IRB Authority

The IRB derives its authority from the UNC-Chapel Hill policy, as cited in Section SOP 101.2.2. Under the federal regulations, IRBs have the authority:

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

The IRB functions independently. Attempts to coerce or otherwise unduly influence the actions of the IRB are forbidden by policy, and are to be reported as described in Section 4.7. Likewise, the IRB must remain free from the influence of financial and other organizational interests. No individual with responsibility for the business and financial interests of the organization may serve on the IRB, for example, individuals such as staff from the Office of Sponsored Research, staff from the Office of Industry contracting or other similar individuals. Individuals who are responsible for business development are prohibited from carrying out day-to-day operations of the review process.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the organization such as the Institutional Official or any other administrators. However, those officials may NOT approve research if it has not been approved or has been disapproved by the IRB. Reviewing officials may strengthen requirements and/or conditions or add other modifications before approval or may require approval by an additional ancillary committee. Previously approved research proposals and/or consent forms must be re-approved by the IRB before initiating any changes or modifications that result from such additional reviews/approvals.
2.2 Roles and Responsibilities

2.2.1 Chair of the IRB

The UNC-Chapel Hill Institutional Official (IO), in consultation with the Director of the OHRE, appoints a Chair and may appoint a Co-Chair or Vice Chair of the IRB to serve for a renewable [3-year] terms. Any change in appointment, including reappointment or removal, requires written notification. A Co-Chair’s roles and responsibilities are the same as a Chair.

The IRB Chair should be a highly respected individual, from within the UNC-Chapel Hill fully capable of managing the IRB, and the matters brought before it with fairness and impartiality. The task of making the IRB a respected part of the research community falls primarily on the shoulders of the Chair. The IRB must be perceived to be fair, impartial and immune to pressure by administration, the investigators whose research plans are brought before it, and other committees and professional and nonprofessional offices/sources.

The IRB Chair is responsible for conducting the meetings, conducting expedited reviews and may serve as signatory for correspondence generated by the IRB.

The IRB Chair is authorized to take immediate action to suspend a study or studies if information is presented regarding subject safety or for any other reason where such action would be deemed appropriate. Such action requires subsequent notice to and review by the convened IRB.

The IRB Chair may designate other experienced IRB members to perform duties such as expedited reviews and other IRB functions.

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

The performance of IRB Chair will be reviewed on an annual basis by the OHRE in consultation with the Institutional Official. Feedback from this evaluation will be provided to the Chair. If the Chair is not acting in accordance with the IRB’s mission, or following these policies and procedures, has an undue number of absences, or not fulfilling the responsibilities of the Chair, he/she may be removed.

2.2.2 Vice Chair of the IRB

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

The performance of IRB Vice Chair will be reviewed on an annual basis by the OHRE Director in consultation with the Institutional Official. Feedback from this evaluation will be provided to the Chair. If the Chair is not acting in accordance with the IRB’s mission, or following these policies and procedures, has an undue number of absences, or not fulfilling the responsibilities of the Chair, he/she may be removed.
2.2.3 IRB Members

The role of an IRB member is to ensure that human research activities comply with federal regulations, state and local laws, and organizational policies and procedures, by:

1. Completing member education and training, both initial and on-going (See SOP 301.2.1).
2. Maintaining the confidentiality of IRB deliberations and research review by the IRB.
3. Conducting and documenting reviews of assigned research in a timely fashion.
4. Attending IRB meetings as scheduled.
   a. Members should attend all meetings for which they are scheduled. If a member is unable to attend a scheduled meeting, they should inform the IRB Chair, Vice Chair, or an IRB Office staff member.
   b. If an IRB member is to be absent for an extended period of time, he or she must notify the IRB as soon as possible in advance so that an appropriate alternate/replacement can be obtained. If the member has a designated alternate, the alternate can serve during the primary member’s absence.
5. Recusing self from final deliberations and vote when s/he has a conflict of interest
6. Participating in subcommittees of the IRB if requested and available.
7. Conduct themselves in a professional and collegial manner.

The performance of IRB members will be reviewed on an annual basis by the IRB Chair and the OHRE Director. IRB members will receive formal documented feedback on the results of this review. Members who are not acting in accordance with the IRB’s mission or not following policies and procedures or who have an undue number of absences may be removed.

2.2.4 Alternate members

The appointment and function of alternate members is the same as that for primary IRB members. An alternate’s expertise and perspective should be comparable to those of the primary member. The role of the alternate member is to serve as a voting member of the IRB when the regular member is unavailable to attend a convened meeting. When an alternate member substitutes for a primary member, the alternate member will receive and review the same materials prior to the IRB meeting that the primary member received or would have received.

The IRB roster identifies the primary member(s) or class of members (e.g., physician scientist) for whom each alternate member may substitute. The alternate member will not be counted toward meeting quorum as a voting member unless he/she is substituting for the primary member. The IRB minutes will document when an alternate member replaces a primary member.

Experienced alternate members may be designated by the Chair to conduct expedited reviews.
2.2.5 **Subcommittees of the IRB**

The IRB Chair, in consultation with the OHRE Director, may designate one or more other IRB members to a subcommittee of the IRB to perform duties, as appropriate, and undertake other IRB functions, and to make recommendations to the IRB (e.g., to supplement the IRB’s initial review, continuing review, review of modifications, and/or review of reports of unanticipated problems or of serious or continuing non-compliance). The IRB Chair, in consultation with the OHRE Director, will appoint IRB members to serve on each IRB Subcommittee created under this Section. The number and composition of the IRB Subcommittee members shall depend on the scope of duties delegated by the IRB Chair to such IRB Subcommittee (e.g., making recommendations, conducting an inquiry, etc.). Any such Subcommittee cannot approve research that requires approval at a convened IRB meeting.

2.3 **IRB Membership**

The structure and composition of the UNC-Chapel Hill IRB is appropriate to the amount and nature of the research that is reviewed. Every effort is made to have member representation that has an understanding of the areas of specialty that encompasses most of the research performed at the UNC-Chapel Hill.

The IRB will include members who are knowledgeable about and experienced working with vulnerable populations that typically participate in the UNC-Chapel Hill research.

The IRB must promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects; and possess the professional competence necessary to review specific research activities. The UNC-Chapel Hill has procedures (See SOP 701.2.2.3) that specifically outline the requirements of research plan review by individuals with appropriate scientific or scholarly expertise. A member of the IRB may fill multiple membership position requirements for the IRB.

2.4 **Composition of the IRB**

1. The IRB will have at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the organization.

2. The IRB will be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

3. In addition to possessing the professional competence necessary to review specific research activities, the IRB will be able to ascertain the acceptability of proposed research in terms of organizational commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB will therefore include persons knowledgeable in these areas.

4. If the IRB regularly reviews research that involves a vulnerable category of subjects (e.g.,
children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration will be given to the inclusion of one or more individuals on the IRB, who are knowledgeable about and experienced in working with these subjects.

5. Every nondiscriminatory effort will be made to ensure that the IRB does not consist entirely of men or entirely of women, including the organization's consideration of qualified persons of both sexes, so long as no selection is made to the IRB solely on the basis of gender. The IRB shall not consist entirely of members of one profession.

6. The IRB includes at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

7. The IRB includes at least one member who is not otherwise affiliated with the organization and who is not part of the immediate family of a person who is affiliated with the organization.

8. The IRB includes at least one member who represents the general perspective of participants.

9. One member may satisfy more than one membership category.

10. The IRB Chair and Vice-Chair are voting members of the IRB.

11. The Director and staff of the UNC-Chapel Hill IRB Office may be voting members of the IRB.

On an annual basis, the IRB Chairs and the OHRE Director shall review the membership and composition of the IRB to determine if they continue to meet regulatory and organizational requirements. Members will receive documented feedback on their performance as reviewers following this annual review.

2.5 Appointment of Members to the IRB

When the IRB Chair, Vice Chair and/or the Director of the IRB Office, identifies a need for a new, replacement, or alternate member, they send the names of candidates to the IRB Office. Department Chairs and others may forward nominations to the Institutional Official or to the OHRE Director.

The final decision in selecting a new member is made by the Institutional Official, in consultation with the OHRE Director and IRB Chair.

Initial appointments are made for a one-year term. Subsequent appointments are made for a renewable three-year period of service. Any change in appointment, including reappointment or removal before the end of a member’s term, requires written notification. Members may resign by written notification to the Chair, Manager or Director.

2.6 IRB Registration Updates

Changes in IRB membership will be reported to FDA and OHRP as follows:
1. A UNC-Chapel Hill decision to disband a registered IRB that it is operating will be reported in writing within 30 days after permanent cessation of the IRB's review of DHHS-conducted or -supported research.

2. If an FDA-regulated IRB decides to review additional types of FDA-regulated products (e.g., to review device studies if it only reviewed drug studies previously) or to discontinue reviewing clinical investigations regulated by FDA, it must report this within 30 days of the change.

3. Within 90 days after changes regarding the contact person who provided the IRB registration information or the IRB Chair.

4. To register any additional IRB before it is designated under an FWA and reviews research conducted or supported by DHHS or regulated by FDA.

5. Within 90 days of a change in the membership roster if that IRB is designated under an FWA.

2.7 Use of Consultants

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

Written statements from consultants will be kept in the IRB records. Key information provided by consultants at meetings will be documented in the minutes. Written reviews provided by the outside reviewer will be filed with the study records.

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

The consultant’s findings will be presented to the convened board for consideration either in person or in writing. If in attendance, these individuals will provide consultation and may assist in the deliberation, but may not participate in the vote.

Ad hoc or informal consultations requested by individual members (rather than the convened board) will be processed by the IRB Office in a manner that protects the investigator’s confidentiality and is in compliance with the IRB conflict of interest policy.

2.8 Liability Coverage for IRB Members

The UNC-Chapel Hill insurance coverage applies to employees and any other person authorized to act on behalf of the UNC-Chapel Hill for acts or omissions within the scope of their employment or authorized activity.
2.9 Reporting and Investigation of Allegations of Undue Influence

If an IRB Chair, member, or staff person feels that the IRB has been unduly influenced by any party, they shall make a confidential report to the OHRE Director or Institutional Official (IO), depending on the circumstances. The IO will ensure that a thorough investigation is conducted and if the allegation is determined valid, that corrective action is taken to prevent additional occurrences. In the event that the allegation is regarding the IO, the matter will be referred to Vice Chancellor for Research for investigation and any necessary action.

Undue influence means attempting to interfere with a normal functioning and decision making of the IRB or to influence an IRB member of staff, or any other member of the research team outside of the establish processes or normal and accepted methods in order to obtain a particular result, decision or action by the IRB or one of its members or staff.

The HRPP Office Director or IO ensure that a thorough investigation is conducted, and if the allegation is determined valid, that corrective action is taken to prevent additional occurrences.
1 Purpose

All non-exempt human subjects research must be reviewed by the IRB. The first step in determining whether research must be reviewed is to determine whether it meets the regulatory definition of human subjects research.

2 Procedure

2.1 Initial Determination by Investigator

The responsibility for initial determination whether an activity constitutes human subject research rests with the investigator. The investigator should make this determination based on the definitions of “human subject” and “research” in SOP 101.3. Because they will be held responsible if the determination is not correct, investigators are urged to request a confirmation that an activity does not constitute human subject research from the OHRE. The request must be made through IRBIS using the online form that guides them through the determination as to whether their project is human subjects research or not. If not, they can get a “Not Human Subjects Research” letter from the IRB. If so, they go on to complete the application. All requests must include sufficient description of the activity and the rationale for the investigator’s initial determination.

2.2 Determinations by the OHRE

Determinations whether an activity constitutes human subject research will be made according to the definitions in SOP 101.3. Determinations regarding activities that are either clearly human subject research or clearly not human subject research, may be made by the IRB Analysts. Determinations regarding less clear-cut activities will be referred to the IRB Chair, who may make the determination or refer the matter to the full IRB.

Documentation of all determinations made through the OHRE will be recorded and maintained in IRBIS.
1 Purpose

All research using human subjects must be approved by the University of North Carolina at Chapel Hill (UNC-Chapel Hill). However, certain categories of human subject research are exempt from IRB approval. Exempt research is subject to review for determination of exemption status. At the UNC-Chapel Hill exemptions are reviewed IRB Staff, and granted by an IRB Chair or designee.

Individuals involved in making the determination of an IRB exempt status of a proposed research project cannot be involved in the proposed research. Reviewers must not have any apparent conflict of interest. Identification of individuals designated to conduct exempt determinations will be made in writing.

Exempt research fulfills the organization’s ethical standards, such as:

- The research holds out no more than minimal risk to subjects.
- Selection of subjects is equitable.
- If there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of the data.
- There are adequate provisions to maintain the privacy interests of subjects.

2 Procedure

2.1 Exemption Determinations

Exemptions are determined or granted, rather than approved. Exempt studies are exempt from the Common Rule [45 CFR 46] (i.e., FWA, IRB approval and full research consent are not required). They do require a determination/confirmation of exemption status. Although exempt research is not covered by the federal regulations, this research is not exempt from ethical considerations, such as honoring the principles described in the Belmont Report. The individual/s making the determination of exemption will determine whether to require additional protections for subjects in keeping with ethical principles (e.g., requiring disclosure/consent, etc.).

Records of exemption actions will be maintained in accordance with SOP 1001.
Changes to an exempted study may render it no longer exempt. Decision charts published by OHRP may assist the IRB in determining level of IRB review needed: 
http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm

2.2 Limitations on Exemptions

The following limitations on exemptions apply to research conducted or supported by HHS:

Children: The exemption for research involving survey or interview procedures or observations of public behavior (#2) does NOT apply to research in children, except for research involving observations of public behavior when the investigator does not participate in the activities being observed.

Prisoners: Exemptions do NOT apply. IRB review is required.

2.3 Categories of Exempt Research

With the above-referenced limitations, research activities not regulated by the FDA (see Section 2.4 for FDA Exemptions) in which the only involvement of human subjects are determined to be in one or more of the following categories are exempt from IRB approval:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, 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.

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 subject’s financial standing, employability, or reputation.

3. Research 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), if:
   (i) the human subjects are elected or appointed public officials or candidates for public office; or
   (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. Research 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.

NOTE: In order to be eligible for this exemption, all of the materials have to exist at the time the research is proposed.

5. Research and demonstration projects which are conducted by or subject to the approval of federal department or agency heads, and which are designed to study, evaluate, or otherwise examine:
   (i) Public benefit or service programs;
   (ii) Procedures for obtaining benefits or services under those programs;
   (iii) Possible changes in or alternatives to those programs or procedures; or
   (iv) Possible changes in methods or levels of payment for benefits or services under those programs.

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).

The research demonstration project must be conducted pursuant to specific federal statutory authority, there must be no statutory requirements of IRB review, the research must not involve significant physical invasions or intrusions upon the privacy of subjects, and the exemption must be invoked only with authorization or concurrence by the federal funding agency.

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

2.4 Procedures for Exemption Determination

In order to obtain an exemption determination, investigators must submit:
   1. Completed Request Exemption section of IRBIS application;
   2. All recruitment materials (e.g., letter of invitation, recruitment script, flyer);
   3. Consent form/disclosure/information sheet (when appropriate);
   4. All surveys, questionnaires, instruments, etc.;
5. Confirmation that permission will be obtained from each non-UNC-Chapel Hill site of performance;

6. If sponsored/funded, one copy of the grant application(s) and/or contract; and

7. Verification of current human research protection training for all members of the research team, including the faculty advisor.

The IRB Analyst or IRB reviewer reviews all requests for exemptions and determines whether the request meets the criteria for exempt research.

To document the reviewer’s determination of the request for exempt research, the reviewer completes the Exemption Determination Form. The reviewer verifies on the form whether the submission meets the definition of human subject research. If the request meets the definition of human subject research, the reviewer then determines whether or not the research is eligible for exemption. Although exempt research is not covered by the federal regulations, this research is not exempt from the ethical guidelines of the Belmont Report.

The individual making the determination of exemption will determine whether to require additional protections for subjects in keeping with the guidelines of the Belmont Report.

If there are interactions with participants, the reviewer 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

The reviewer indicates whether the request for exemption was approved or denied, and if approved, the rationale for the determination and category/s under which it was permitted. The exempt application, review form, and determination letter are recorded and maintained in the same manner and for the same length of time as other IRB review documentation.

Once exemption review is completed, IRB staff will send written notification of the results of the review to the investigator.

Exempt determinations do not have a termination date. After a determination is made, the reviewer will file the study in the archives. Investigators must report any proposed modification to the research during the course of the exempt study if the modification could impact the exemption determination. Investigators should notify the IRB office when an exempt research project is complete so that the organization can maintain an accurate database of active research.
1 Purpose

The IRB will review and ensure that University of North Carolina at Chapel Hill (UNC-Chapel Hill) research involving human subjects meets all required ethical and regulatory criteria for initial and continuing review and any modifications of approved research. The IRB may conduct their review using the following review methods:

- Expedited Review
- Review by Convened IRB

The following describes the procedures required for the review of research by the on-site IRB. (See SOP 901 for a description of the procedures for review of research by the off-site/external IRBs.)

2 Procedure

2.1 Expedited Review

An IRB may use the expedited review procedure to review either or both of the following:

1. Some or all of the research appearing on the list of categories of research eligible for expedited review and found by the reviewer(s) to involve no more than minimal risk.

2. Minor changes in previously approved research during the period (of one year or less) for which approval is authorized. Note: review of minor changes does not alter the end-date of study approval.

The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review—expedited or convened—used by the IRB.

2.1.1 Categories of Research Eligible for Expedited Review

The UNC-Chapel Hill applies the categories of research eligible for expedited review, which were published in the Federal Register notice 63 FR 60364-60367, November 9, 1998.

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

The categories in this list apply regardless of the age of subjects, except as noted in category 2.
The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

The expedited review procedure may not be used for classified research involving human subjects.

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

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

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
   (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
   (b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week. (Note: Children are defined as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.)

(3) Prospective collection of biological specimens for research purposes by noninvasive means.
   Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncanulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i)
mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization; (k) vaginal swabs that do not go beyond the cervical os; rectal swabs that do not go beyond the rectum; and nasal swabs that do not go beyond the nares.

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

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject’s privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46 101(b)(2) and b(3). This listing refers only to research that is not exempt.)

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

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

Categories 8 and 9 apply only to continuing review.

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

(a) Where (i) the research at the UNC-Chapel Hill is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects (Note: “Long-term follow-up” includes research interactions that involve no more than minimal risk to subjects (e.g., quality of life surveys); and collection of follow-up data from procedures or interventions that would
have been done as part of routine clinical practice to monitor a subject for disease progression or recurrence, regardless of whether the procedures or interventions are described in the research study, but not interventions that would not have been performed for clinical purposes, even if the research interventions involve no more than minimal risk.); or

(b) Where no subjects have ever been enrolled at the UNC-Chapel Hill and no additional risks have been identified (Note: “no additional risks have been identified” means that neither the investigator nor the IRB has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB’s most recent prior review.); or

(c) Where the remaining research activities at the UNC-Chapel Hill are limited to data analysis. (Note: Simply maintaining individually identifiable private information without using, studying, or analyzing such information is not human subject research and thus does not require continuing review.

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

- The research is not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE);
- Expedited review categories (2) through (8) do not apply to the research;
- The IRB has determined and documented at a convened meeting that the research, or the remaining research activity involving human subjects, involves no greater than minimal risk to the subjects; and
- No additional risks of the research have been identified. (Note: “no additional risks have been identified” means that neither the investigator nor the IRB has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB’s most recent prior review.)

2.1.2 Expedited Review Procedures

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

As warranted, the Chair, in collaboration with the Office of Human Research Ethics (OHRE) Director will designate a list of IRB members eligible to conduct expedited review of submissions. The designees must be experienced voting members or alternate members of the IRB. Selected reviewers will have the qualifications, experience and knowledge in types of research to be reviewed, as well as be knowledgeable of the requirements to approve research under expedited review (i.e., CIP certified members or non-CIP certified members who have completed training and demonstrated proficiency). IRB members with a conflict of interest in the research may not conduct the expedited review.
When reviewing research under an expedited review procedure, the IRB Chair, or designated IRB member(s), will receive and review all documentation that would normally be submitted for a full-board review. This requirement applies to all categories of submissions including initial reviews, continuing reviews, and modifications. The reviewer will determine and document the regulatory criteria allowing use of the expedited review procedure in IRBIS, the electronic application.

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

In reviewing the research, the reviewers will follow the Review Procedures described in Section 2.3 (Criteria for IRB Approval of Research) and may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure by the convened IRB. If modifications are required, the OHRE staff will inform the investigator in writing.

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

2.1.3 Informing the IRB

All members of the IRB will be apprised of all expedited review approvals by means of a list in the agenda for the next scheduled meeting. Any IRB member can request to review any study by contacting the OHRE.

2.2 Convened IRB Meetings

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

2.2.1 IRB Meeting Schedule

The IRB meets on a regular basis throughout the year. Each IRB generally meets once a month on a regularly scheduled day (e.g., first Monday of each month). The schedule for the IRB may vary due to holidays or lack of quorum. The schedule for IRB meetings is posted on the IRB website (ohre.unc.edu). Special meetings may be called at any time by the Chair or OHRE Director.
2.2.2 Preliminary Review

The IRB Analyst will perform a preliminary review of all submissions for determination of completeness and accuracy, including an informed consent checklist, when applicable. Only complete submissions will be placed on the IRB agenda for review. The investigator will be informed either by e-mail, phone or in person of missing materials and the necessary date of receipt for inclusion on the agenda. If an investigator is submitting for the first time or is not well-versed in the submission procedures, consultations can be arranged with IRB staff.

The IRB defers to another meeting, IRB, or obtains consultation if there is not at least one person on the IRB with appropriate scientific or scholarly expertise or other expertise or knowledge to conduct an in-depth review of the protocol.

2.2.3 Primary and Secondary Reviewers

After it has been determined that the submission is complete, the IRB Analyst with the assistance of the IRB Chair, as needed, will assign submissions for review paying close attention to the subject matter of the research, the potential reviewer’s area/s of expertise and representation for any vulnerable populations involved in the research. The “primary reviewer” will be assigned to each submission and have access to and review the full submission materials. A reviewer may be assigned several submissions or other items for review. When the IRB is presented with a research study which may be outside of the knowledge base or representative capacity of the IRB members, an outside consultant will be sought (See SOP 401.7, Use of Consultants). Research studies for which appropriate expertise cannot be obtained for a given meeting will be deferred to another meeting when appropriate expertise is available.

Primary and secondary reviewers are responsible for:

1. Having a thorough knowledge of all of the details of the proposed research.
2. Performing an in-depth review of the proposed research.
3. Beginning the discussion of the proposed research at the convened meeting, by summarizing the proposed research and leading the IRB through the regulatory criteria for approval (See Section 2.3, Criteria for IRB Approval of Research).
4. Making suggestions for changes to the proposed research, where applicable.
5. Performing an in-depth review of the proposed research, including review of any relevant grant applications and/or protocol.
6. Completing the applicable IRB Reviewer Checklist.

A “secondary” reviewer may be assigned in addition to the primary reviewer. A secondary reviewer will be assigned to review the full submission materials.

All IRB members have access to and are expected to review all studies, not just those assigned as primary or secondary reviewer.
When it can be anticipated that the primary reviewer may be absent from the meeting, a new primary reviewer may be assigned, providing that they have sufficient time to review the materials in advance of the meeting. Additionally, an absent reviewer can submit their written comments for presentation at the convened meeting. If an absent reviewer submits comments, those can indicate a recommendation regarding approval, but such recommendation will not be counted as a vote.

2.2.4 Materials received by the IRB

All required materials need to be submitted to the OHRE approximately two weeks prior to the convened meeting for inclusion on the IRB agenda. The meeting agenda will be prepared by the IRB analyst in consultation, as needed, with the IRB Chair. All IRB members receive the IRB agenda, prior meeting minutes, applicable business items, and research submission materials approximately 10 business days before the scheduled meeting to allow sufficient time for the review process. Continuing education materials are emailed to all IRB members on the first day of each month.

Each IRB member reviews the following documentation, as applicable, for all studies on the agenda:

- A Protocol/Research Plan Summary or the complete Protocol
- The Study Application
- Proposed Consent / Parental Permission / Assent Form(s)
- Recruitment materials including advertisements intended to be seen or heard by potential subjects

The primary and secondary reviewers review, in addition to the above, (1) the full protocol/research plan, (2) any relevant grant applications; and, (3) the investigator’s brochure (when one exists) and/or other risk information. Additionally, for DHHS-supported multicenter clinical trials, the primary reviewer should receive and review a copy of the DHHS-approved sample informed consent document(s) (when one exists) and the complete DHHS-approved protocol/research plan (when one exists). All members have access to all study materials described above.

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

Primary and secondary reviewers will use the appropriate UNC-Chapel Hill IRB Reviewer Checklist as a guide to completing and documenting their review.

2.2.5 Quorum

A quorum of the IRB consists of a majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area. When research involving an investigational new drug is on the agenda for review, a physician should be included in the quorum. At meetings of the IRB, a quorum must be established and maintained.
for the deliberation and vote on all matters requiring a vote.

The IRB Chair, with the assistance of the IRB staff, will confirm that quorum is present before calling the meeting to order. The IRB Chair, with the assistance of the IRB staff, will be responsible to ensure that the IRB meeting remains appropriately convened. If a quorum is not maintained, either by losing a majority of the members, losing all non-scientific members or another required member, the IRB cannot take further actions or vote on regulatory determinations until quorum is restored, even if half of the members are still present. The IRB Staff will monitor the arrival and departure for all IRB members and notify the IRB Chair if a quorum is not present. An attendance/vote card is completed by the IRB Staff to determine and document whether the IRB meeting is appropriately convened and quorum is maintained.

It is generally expected that at least one unaffiliated member and at least one member who represents the general perspective of participants (i.e., the “non-scientist”) will be present at all IRB meetings. An individual may serve as both the unaffiliated and non-scientist member. The IRB may, on occasion, meet without representation of the unaffiliated member; however, this should be the exception.

If the IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or persons with impaired decision-making capacity, one or more individuals (e.g., IRB members, alternate members, or consultants) who are knowledgeable about and experienced with those subjects should be present during the review of the research.

IRB members are considered present and participating at a duly convened IRB meeting when either physically present or participating through electronic means (e.g., teleconferencing or video conferencing) that permits them to listen to and speak during IRB deliberations and voting. Whether or not physically present, the IRB member must have received all pertinent materials prior to the meeting and must be able to participate actively and equally in all discussions.

Opinions of absent members that are transmitted by mail, telephone, facsimile or e-mail may be considered by the attending IRB members but may not be counted as votes or to satisfy the quorum for convened meetings.

### 2.2.6 Meeting Procedures

The IRB Chair will call the meeting to order, once it has been determined that a quorum is in place. The Chair will remind IRB members to recuse themselves from the discussion and votes by leaving the room when they have a conflict. The Chair will provide an opportunity for members to discuss the minutes from the prior meeting and determine if there are any revisions/corrections to be made. If there are no changes to be made, the minutes will be accepted as presented and considered final. If major revisions/corrections are necessary, the minutes will be amended and presented at the following IRB meeting.

The IRB reviews all submissions for initial and continuing review, as well as requests for modifications. The Primary Reviewer will present an overview of the research and assist the
Chair in leading the IRB through the completion of the regulatory criteria for approval. In order for the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

It is the responsibility of the IRB analyst to record the proceedings of the session. In addition, the IRB Office Assistant and IRB analyst are responsible for taking Minutes at each IRB meeting.

2.2.7 Guests

Investigators and research staff may be invited to the IRB meeting, at the discretion of the IRB, to make a brief presentation or to answer questions about proposed or ongoing research. Attendance is generally reserved for studies that are under reconsideration. The investigator/research staff may not be present for the deliberations or vote on the research.

All meeting guests will be listed on the Attendance/Vote Card and documented in the meeting minutes.

The OHRE Director and staff may attend IRB meetings and may participate in the IRB discussion and deliberations, but may not vote unless they have been appointed as an IRB committee member.

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

2.3 Criteria for IRB Approval of Research

In order for the IRB to approve human subjects research, either through expedited review or by the convened IRB, it must determine that the following requirements are satisfied. These criteria apply to all categories of IRB reviews including initial reviews, continuing reviews, and modifications of previously approved research.

1) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally
disable persons, or economically or educationally disadvantaged persons.

4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by the Federal Regulations [45 CFR 46.116].

5) Informed consent will be appropriately documented, in accordance with, and to the extent required by the Federal Regulations [45 CFR 46.117].

6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

8) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

2.3.1 Risk/Benefit Assessment

The goal of the assessment is to ensure that the risks to research subjects posed by participation in the research are justified by the anticipated benefits to the subjects or society. Toward that end, the IRB must:

- Judge whether the anticipated benefit, either of new knowledge or of improved health or other direct benefit for the research subjects, justifies asking any person to undertake the risks; and
- Disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

The assessment of the risks and benefits of proposed research involves a series of steps:

1. Identify the risks associated with the research, as distinguished from the risks of activities, diagnostic tests, treatments, or therapies the subjects would receive even if not participating in research;

2. Determine whether the risks will be minimized to the extent possible by evaluating the necessity of procedures that impart risk and whether the data could be gained by procedures that are already being performed for other purposes or by alternative procedures that impart less risk;

3. Identify the anticipated benefits to be derived from the research, both direct benefits to subjects and possible benefits to society, science and others;

4. Determine whether the risks are reasonable in relation to the benefits, if any, and assess the importance of the knowledge to be gained;
In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research - as distinguished from risks and benefits subjects would receive even if not participating in the research.

In addition to evaluation of the risks in the research, the IRB determines, based on the materials submitted by the investigator, that research studies have the resources necessary to protect participants, such as adequate time for the researchers to conduct and complete the research, adequate number of qualified staff, adequate facilities, access to a population that will allow recruitment of the necessary number of participants, availability of medical or psychosocial resources that participants might need as a consequence of the research.

The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks and benefits that fall within the purview of its responsibility.

2.3.2 Scientific or Scholarly Review

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

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

In making this determination, the IRB may draw on its own knowledge and expertise, and/or the IRB may draw on the knowledge and expertise of others, such as reviews by a funding agency, or departmental review. When scientific or scholarly review is conducted by an individual or entity external to the IRB, documentation that the above questions were considered must be provided to the IRB for review and consideration.

Scientific or scholarly review is documented and provided to the IRB by the Scientific Review Committee for all biomedical research conducted at the University of North Carolina at Chapel Hill involving procedures that pose greater than minimal risk that have not received external independent scientific/scholarly review or multi-center industry-sponsored research.

Scientific or scholarly review of research not meeting the above criteria can be delegated to a departmental or other appropriate review committee.

2.3.3 Equitable Selection of Subjects

The IRB determines by reviewing the application, protocol/research plan and other materials that the selection of subjects is equitable with respect to gender, age, class, etc. The IRB will not approve a study that does not provide adequately for the equitable selection of subjects or has not provided an appropriate scientific and ethical justification for excluding classes of persons who might benefit from the research. In making this determination, the IRB evaluates:

- The purposes of the research;
- The setting in which the research occurs;
• Scientific and ethical justification for including vulnerable populations such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons;

• The scientific and ethical justification for excluding classes of persons who might benefit from the research; and

• The inclusion/exclusion criteria, and the procedures/materials intended for use for the identification and recruitment of potential subjects.

At the time of the continuing review the IRB will determine that the investigator has followed the subject selection criteria that was originally set forth at the time of the initial IRB review and approval.

2.3.4 Recruitment of Subjects

The investigator will provide the IRB with a plan for recruitment of all potential subjects. All recruiting materials will be submitted to the IRB, including advertisements, flyers, scripts, information sheets and brochures. The IRB should ensure that the recruitment plan and materials appropriately protect the rights and welfare of the prospective subjects (e.g., do not present undue influence). See Section 2.4.10 for a discussion of IRB review of advertisements and Section 2.4.11 for a discussion of IRB review of payments.

2.3.5 Informed Consent

The IRB will ensure that informed consent will be sought from each prospective subject or the subject’s legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.20. In addition, the IRB will ensure that informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27. The IRB will ensure, as part of its review, that the information in the consent document and process is consistent with the research plan, and, when applicable, the HIPAA authorization. See SOP 1101 for detailed policies on informed consent.

2.3.6 Data and Safety Monitoring

For all research that is more than minimal risk, the investigator should submit a data and safety monitoring plan. The initial plan submitted to the IRB should describe the procedures for safety monitoring, reporting of unanticipated problems involving risks to subjects or others, descriptions of interim safety reviews and the procedures planned for transmitting the monitoring results to the IRB. When applicable, the monitoring plan should include information regarding an independent Data and Safety Monitoring Board (DSMB).

The IRB reviews the safety monitoring plan and determines if it makes adequate provision for monitoring the reactions of subjects and the collection of data to ensure the safety of subjects and address problems that may arise over the course of the study. If a plan was not submitted, the IRB determines whether or not a plan is required, and, depending on the circumstances, what the plan should include. The overall elements of the monitoring plan may vary depending on the potential risks, complexity, and nature of the research study.
The factors the IRB will consider in determining whether the safety monitoring plan is adequate for the research are as follows:

1. Monitoring is commensurate with the nature, complexity, size and risk involved.
2. Monitoring is timely. Frequency should be commensurate with risk. Conclusions are reported to the IRB.
3. For low risk studies, continuous, close monitoring by the study investigator or an independent individual may be an adequate and appropriate format for monitoring, with prompt reporting of problems to the IRB, sponsor and regulatory bodies as appropriate.
4. A written Data and Safety Monitoring Plan (DSMP) prospectively identifies and documents monitoring activities intended to protect the safety of the subjects, the validity of the data and the integrity of the research study. The DSMP may also identify when to terminate a subject’s participation (i.e. individual stopping rules) and/or the appropriate termination of a study (i.e. study stopping rules). The nature, size, risk, and complexity of the study will determine whether and how to address the following seven elements within the DSMP:
   - Subject Safety – monitoring is conducted to avoid or minimize risks (i.e. physical, psychological or social).
   - Data Integrity – monitoring is conducted to assure data is accurate and complete. Monitoring of data assures adherence to the approved clinical study.
   - Subject Privacy – monitoring is conducted to assure individual’s rights are protected.
   - Data Confidentiality – monitoring is conducted to assure data is secured.
   - Product Accountability – monitoring is conducted to assure drug(s) or device(s) are tracked and accounted for.
   - Study Documentation – monitoring is conducted to assure that required documentation and reports are on file, accurate, and complete.
   - Study Coordination – monitoring is conducted to assure that investigator delegation and communication with the research team is planned and systematic.
5. For a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), the plan should describe:
   - The composition of the board or committee. Generally, a DSMB should be composed of experts in all scientific disciplines needed to interpret the data and ensure subject safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease/condition and treatment under study should be part of the monitoring group or be available if warranted.
   - Frequency and content of meeting reports
• The frequency and character of monitoring meetings (e.g., open or closed, public or private)

• The Charter should be provided, when one exists

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

2.3.7 Privacy and Confidentiality

The IRB will determine whether adequate procedures are in place to protect the privacy of subjects and to maintain the confidentiality of the data.

2.3.7.1 Definitions

Privacy. Having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. It is the state or condition of being free from unauthorized intrusion, being observed or disturbed by other people.

Confidentiality. Methods used to ensure that information obtained by investigators about subjects is not improperly divulged.

Private information. Information that has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

Sensitive Information. Data or information, on any storage media or in any form or format, which requires protection due to the risk of harm that could result from inadvertent or deliberate disclosure, unauthorized access, misuse, alteration, or loss or destruction of the information (e.g., could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject’s financial standing, employability, or reputation).

Identifiable information. Information where the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

2.3.7.2 Privacy

The IRB must determine whether the activities in the research appropriately protect the privacy of potential and actual subjects. In order to make that determination, the IRB must obtain information regarding how the investigators plan to access subjects or subjects’ private, identifiable information and the subjects’ expectations of privacy in the situation. Investigators must have appropriate authorization to access the subjects or the subjects’ information.
In developing strategies for the protection of subjects’ privacy, consideration is given to:

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

2.3.7.3 Confidentiality

The IRB must determine if appropriate protections are in place to minimize the likelihood that information about subjects will be inappropriately divulged. Safeguards designed to protect confidentiality should be commensurate with the potential of harm from unauthorized, inappropriate or unintentional disclosure.

At the time of initial review, continuing review and with any requests for modification, the IRB assesses whether there are adequate provisions to protect data confidentiality. The IRB does this through the evaluation of the methods used to obtain, record, share, and store information about individuals who may be recruited to participate in studies and about subjects. The investigator will provide the IRB with a plan regarding the procedures to be taken to protect the confidentiality of research data and sensitive information. Additionally, the investigator will provide information regarding information security procedures and plans to address the protection of paper documents, other physical media (e.g., audio or videotapes), and electronic data and information including the use, maintenance, storage, and transmission of information. The IRB will review all information received from the investigator and determine whether or not the confidentiality of research data is sufficiently protected. In some cases, the IRB may also require that a Certificate of Confidentiality (CoC) be obtained to additionally protect research data (See AOP 2001.9 for additional information about the use of a CoC.)

In reviewing confidentiality protections, the IRB shall consider whether or not the data or other information accessed or gathered for research purposes is sensitive and the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It shall evaluate the effectiveness of proposed de-identification techniques, coding systems, encryption methods, methods of transmission, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections. In reviewing confidentiality protections, the IRB shall also consider regulations and organizational requirements and policies regarding the use of information and information security.
Research regulated by the FDA that involves the use of electronic data collection/storage systems must comply with the requirements of 21 CFR Part 11.

2.3.8 Vulnerable Populations

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

For an extensive discussion about the IRB’s review and approval process for individual populations of vulnerable subjects, please refer to SOP 1201.

2.4 Additional Considerations

2.4.1 Determination of Risk

At the time of initial and continuing review, the IRB will make a determination regarding the risks associated with the research plan. Risks associated with the research will generally be classified as either “minimal” or “greater than minimal” with additional classifications as required by the various subparts or FDA regulations. Risk determinations may vary over the life of a research plan depending on the procedures and risks that subjects will be exposed to as the research progresses. The level of risk associated with the research influences eligibility for expedited review. The meeting minutes will reflect the convened IRB’s determination regarding risk levels; expedited reviewers will document the determination of risk level in IRBIS.

2.4.2 Period of Approval

At the time of initial review and at continuing review, the IRB will make a determination regarding the period of approval. All studies will be reviewed by the IRB at intervals appropriate to the degree of risk but no less than once per year. In some circumstances, a shorter review interval (e.g., semi-annually, quarterly, or after accrual of a specific number of participants) may be required (see below). The meeting minutes will reflect the convened IRB’s determination regarding review frequency; expedited reviewers will document the determination of risk level in IRBIS.

IRB approval is considered to have lapsed at midnight on the expiration date of the approval (i.e., the expiration date is the last day research can be conducted). For a new study reviewed by the IRB, the approval commences on the date that the IRB conducts its final review of the study; that is, the date that the convened IRB or expedited reviewer approves the research or the date (“effective date”) that it is verified that the requirements of the IRB have been satisfied following an action of “Conditions Required for Approval”. The expiration date of the initial approval period, which is the date by which the first continuing review must occur, may be as late as one year after the date of convened IRB approval (with or without conditions).
For subsequent continuing reviews of a research study subject to convened board review, the date the convened IRB or the date that the expedited reviewer conducts continuing review and approves the study (with or without conditions) determines the latest permissible date of the next continuing review.

The approval date and approval expiration date are clearly noted on IRB determination letters and must be strictly adhered to. Investigators should allow sufficient time for development and review of continuing review submissions.

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

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur by midnight of the date when IRB approval expires.

### 2.4.3 Review More Often Than Annually

The following factors will be considered when determining which studies require review more frequently than on an annual basis:

1. The probability and magnitude of anticipated risks to subjects.
2. The likely medical/psychological/social/legal/educational condition of the proposed subjects.
3. The overall qualifications of the investigator and other members of the research team.
4. The specific experience of the investigator and other members of the research team in conducting similar research.
5. The nature and frequency of adverse events observed in similar research at this and other institutions.
6. The novelty of the research making unanticipated adverse events/unanticipated problems more likely.
7. The involvement of especially vulnerable populations likely to be subject to undue influence or coercion (e.g., terminally ill)
8. A history of serious or continuing non-compliance on the part of the investigator.
9. Any other factors that the IRB deems relevant.

In specifying an approval period of less than one year, the IRB may define the period with either a time interval or a maximum number of subjects either studied or enrolled. If a maximum number of subjects studied or enrolled is used to define the approval period, it is understood that the approval period in no case can exceed one year and that the number of subjects studied or enrolled determines the approval period only when that number of subjects is studied or enrolled in less than one year. If an approval period of less than one year is specified by the IRB, the reason for more frequent review must be documented in the
2.4.4 Independent Verification That No Material Changes Have Occurred

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB use sources other than the investigator to independently verify that no material changes occurred during the IRB-designated approval period.

The IRB will determine the need for verification from outside sources on a case-by-case basis. The following factors will be considered when determining which studies require independent verification:

1. The probability and magnitude of anticipated risks to subjects.
2. The likely medical/psychological/social/legal/educational condition of the proposed subjects.
3. The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.
4. Concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources.
5. Investigators who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB.
6. Research without a routine monitoring plan.
7. Any other factors the IRB deems verification from outside sources is relevant.

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

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken (see SOP 1402 on Non-compliance).

2.4.5 Consent Monitoring

In reviewing the adequacy of informed consent procedures for proposed research, the IRB may on occasion determine that special monitoring of the consent process by an impartial observer (e.g., consent monitor) is required in order to reduce the possibility of coercion and undue influence, ensure that the approved consent process is being followed, or ensure that subjects are truly giving informed consent.

Such monitoring may be particularly warranted for:

1. High risk studies;
2. Studies that involve particularly complicated procedures or interventions;
3. Studies involving highly vulnerable populations (e.g., ICU patients, children who are wards);
4. Studies involving study staff with minimal experience in administering consent to potential study participants; or
5. Other situations when the IRB has concerns that consent process may not be/is not being conducted appropriately (e.g., prior investigator non-compliance, etc.).

Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

The responsible party for conducting this activity will be the IRB monitor (i.e., an unbiased observer appointed by the Director of the Office of Human Research Ethics/IRB). The Principal Investigator if responsible for complying with this policy.

2.4.5.1 Consent Monitoring Procedure

1. The IRB monitor may or may not provide advance notice to the Principal investigator or other members of the research team. When research is being conducted in the Clinical and Translational Research Center (CTRC), the IRB monitor will review the CTRC schedule and select study visits during which informed consent is scheduled to occur.

2. If the Principal investigator is notified in advance, he/she must respond to the IRB’s request in writing (i.e., email) within 10 working days.

3. Prior to the consent monitoring process, the IRB monitor will introduce him/herself to the potential participant, explain the reason for his/her presence and obtain the participant’s verbal permission for observing the consent process.

4. During the monitoring process:
   a. The IRB monitor will monitor the process of informed consent conducted by the PI (or designee) with the prospective research participant and/or the participant’s legally authorized representative/guardian.
   b. The IRB monitor will collect data on the informed consent process by employing a variety of methods, including but not limited to, a physical presence (monitoring) during the consent process and/or employing the use of open-ended questions to evaluate the effectiveness of the consent process and the use of a monitoring checklist. The IRB monitor will determine whether:
   c. The consent document includes all of the required and applicable additional elements (outlined in 21 CFR 50.25).
   d. The information in the consent document and any other written information was clearly and accurately explained to the participant or the participant’s legally authorized representative/guardian.
e. Adequate time was available to review the research with the participant and/or the participant’s legally authorized representative/guardian.

f. The participant and/or legally authorized representative/guardian were given an opportunity to ask and have their questions answered.

g. The consent process was free of coercion or undue influence.

h. The participant and/or legally authorized representative/guardian comprehended the information that was presented to them. This may be accomplished by soliciting the participant’s and/or participant’s legally authorized representative’s understanding by employing the use of open-ended questions.

i. The information that is given to the participant and/or legally authorized representative/guardian was in a language understandable to them.

j. The informed consent was free of exculpatory language.

k. The informed consent process was appropriately documented.

5. Following the monitoring process:

   a. The IRB monitor may discuss any initial observations privately with the individual who conducted the consent process. If the observation indicates that the consent process is not legally effective, the participant must be re-consented or may not be entered into the research, in which case the Principal Investigator will be promptly notified.

   b. The IRB monitor will determine if additional education is required and/or if a second consent monitor visit should be scheduled.

   c. Within 10 business days, the IRB monitor will prepare a written summary of the consent process and summarize his/her findings and if applicable, recommendations. The report will be shared with the OHRE Director and if applicable, the person(s) who requested the monitoring visit.

   d. The IRB monitor will contact the Investigator (via e-mail) to set up a mutually convenient time to meet to review the findings of the monitoring visit. The written summary will be reviewed during the meeting which will be scheduled no later than 15 business days following the monitoring visit.

2.4.6 Investigator Qualifications

The IRB reviews credentials, curriculum vitae, resumes, or other relevant materials to determine whether investigators and members of the research team, who are external to UNC, are appropriately qualified to conduct the research. The IRB relies upon department approval and other UNC-Chapel Hill processes (e.g., credentialing) to inform this determination when investigators are UNC-Chapel Hill faculty or staff.
2.4.7 Investigator Conflicts of Interest (COI)

The IRB research application asks specific questions regarding the investigator and research team compliance with disclosure requirements and whether or not any COI management plans are in place. As part of its review process, the IRB will make a final determination as to whether any conflict of interest is adequately addressed and protects the human subjects in the research. The IRB has final authority to determine whether the declared COI and the management plan, if any, allow the study to be approved.

2.4.8 Institutional Conflicts of Interest

As with individual conflict of interest, the IRB has final authority to determine whether the Institutional Conflict, the Financial Interest, and the management plan, if any, allow the study to be approved.

2.4.9 Significant New Findings

During the course of research, significant new knowledge or findings about the research, the test article, and/or the condition under study may develop. The investigator must report any significant new findings to the IRB and the IRB will review them with regard to the impact on the subjects’ rights and welfare. Because the new knowledge or findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the IRB may require, during the ongoing review process, that the investigator contact the currently enrolled subjects to inform them of the new information. The IRB will communicate this requirement to the investigator. If the study is still enrolling subjects, the consent document should be updated. IRB may require that the currently enrolled subjects be re-consented or otherwise provided with the new information. The IRB may also require that former subjects be provided with the new information, e.g., if it impacts their rights or welfare.

2.4.10 Advertisements and Recruitment Materials

The IRB must review and approve any and all advertisements prior to posting and/or distribution for studies that are conducted under the purview of the UNC-Chapel Hill.

The IRB will review:

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

This information should be submitted to the IRB with the initial application or, if recruitment is proposed after study approval, as a modification request.
The IRB reviews the material to assure that the material is accurate and is not coercive or unduly optimistic, creating undue influence to the subject to participate. This includes but is not limited to:

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

Recruitment materials should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included:

1. The name and address of the investigator and/or research facility.
2. The condition being studied and/or the purpose of the research.
3. In summary form, the criteria that will be used to determine eligibility for the study.
4. The time or other commitment required of the subjects.
5. The location of the research and the person or office to contact for further information.
6. A clear statement that this is research and not treatment.
7. A brief list of potential benefits (e.g., no-cost health exam).

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

The first contact prospective study subjects make is often with a person who follows a script to determine basic eligibility for the specific study. The IRB should assure the procedures followed adequately protect the rights and welfare of the prospective subjects.
2.4.10.1 Advertising on clinical trial websites

OHRP issued guidance on internet advertising on September 20, 2005. Clinical trial websites that provide only directory listings with basic descriptive information about clinical trials in general do not need to be reviewed by an IRB. Examples of clinical trial listing services that do not need IRB review and approval include the National Institutes of Health (NIH) ClinicalTrials.gov website, the NIH National Cancer Institute's cancer clinical trials listing (Physician Data Query [PDQ]), and the government-sponsored AIDS Clinical Trials Information Service (ACTIS).

In keeping with the DHHS and FDA guidance, the UNC IRB has determined that the IRB review/approval for brief internet advertisements (e.g., listing of studies on department or research website) is not necessary provided that the information is limited to:

- study title
- purpose of the study
- protocol summary
- basic eligibility criteria
- study site location(s), and
- contact information for the study site

When information posted on a clinical trial website goes beyond directory listings with the basic descriptive information given above, such information is considered part of the informed consent process and therefore requires IRB review and approval. *Information exceeding such basic listing information* includes:

- descriptions of clinical trial risks and potential benefits, or
- solicitation of identifiable information from potential research subjects.

2.4.11 Payments to Research Subjects

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

Investigators who wish to pay research subjects must submit to the IRB the amount and schedule of all payments. Investigators should indicate in their research project application the justification for such payment. Such justification should substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject and do not constitute (or appear to constitute) undue pressure on the potential subject to volunteer for the research study.
The IRB must review both the amount of payment and the proposed method and timing of disbursement to assure that neither entails problems of coercion or undue influence.

Credit for payment should be prorated and not be contingent upon the participant completing the entire study. The IRB does not allow the entire payment to be contingent upon completion of the entire study. Any amount paid as bonus for completion of the entire study should not be so great that it could unduly induce subjects to remain in the study when they otherwise would have withdrawn.

The consent form must describe the terms of payment including the amount and schedule of payments and any conditions under which subjects would receive partial payment (e.g., if they withdraw from the study before their participation is completed) or no payment.

The UNC-Chapel Hill Office Disbursement Services requires identifying information to issue checks for payment. A separate Social Security Number collection form informs subjects that they are being asked to provide their Social Security Number for payments in excess of $400/calendar year or for any amount when payment is being issued by the Office of Disbursement Services.

**2.4.11.1 Non-Monetary Gifts and Incentives**

Similar to financial incentives, non-monetary gifts or incentives can also present problems of undue influence or coercion that impact a potential subject’s ability to fully and freely consider participation in research.

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

The IRB will review all gifts and incentives being particularly sensitive to the influence of power or authority, whether perceived or actual, over free decision-making. Overt coercion (e.g., threatening loss of credit, or access to services or programs, to which the potential subjects are otherwise entitled) is never appropriate. Moreover, it must be clear that choosing to not participate will not adversely affect an individual’s relationship with the organization or its staff or the provision of services in any way (e.g., loss of credits or access to programs).

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

**2.4.11.2 Lotteries, raffles and door prizes**

Occasionally, investigators who are not in a position to offer equal compensation to each research subject propose to substitute a drawing as an incentive. For example, an investigator with only $200 to compensate 100 subjects might propose a drawing for two $100 prizes rather than paying each subject $2.00. University research projects may not include distribution of prizes to the research subjects via chances purchased by the human subjects or obtained by them in exchange for something of value (e.g., money, human tissues or blood samples). The
terms used for these purchased chance distributions include “lottery” and “raffle.” The prohibition is pursuant to State law and University policy. A prize distributed by chance where the chance is obtained merely by attendance at an event (sometimes called a “door prize”) and not by the payment of any fee, donation or other consideration is not prohibited by law or University policy.

Regardless of the terminology used, University research should generally not include distribution of incentives to human subjects by chance. This method may represent coercion or undue influence if the incentive is sufficiently valuable. Additionally, the distribution of incentives via chance represents an unequal distribution of the incentive and may be unfair to subjects who will ultimately receive nothing. Generally, rather than conducting a drawing, researchers should provide equitable incentives to each subject, even if such a practice diminishes the value of the incentive. However, use of incentives structured as described above for “door prizes” may be considered by the IRB on a case-by-case basis for research studies of minimal risk and brief duration if the proposed incentives do not have potential for coercion or undue influence and clearly are not distributed in exchange for valuable consideration such as blood or tissue samples or significant time and effort in research participation. The IRB should consult with the Office of University Counsel prior to approval of any incentive distributed by chance. If such an incentive is approved for a given study, consent form language describing the incentive should avoid terms like “lottery” or “raffle.” Acceptable terminology might include a reference to a “drawing based on chance in which each subject has equal odds of receiving [the incentive].”

NCGS §14-309.15 Raffles

2.4.12 State and Local Laws

The IRB considers and adheres to all applicable state and local laws in the jurisdictions where the research is taking place. The HRPP and IRB rely on the UNC-Chapel Hill Counsel for the interpretation and application of North Carolina law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research. The IRB will ensure that consent forms are consistent with applicable state and local laws.
2.5 Possible IRB Actions

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

Conditions Required for Approval. (Also known as approval with stipulations or approval with contingencies.) The research, proposed modification to the previously approved research, or other item is approved but conditions must be satisfied before the approval becomes effective.

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

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

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

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

When the convened IRB approves research with conditions, the IRB Chair (and/or other qualified individual(s)) will review responsive materials from the investigator and determine that the conditions have been satisfied. If the conditions have not been satisfied, or are only partially satisfied, the stipulation is resent to the investigator. No additional stipulations may be added by the expedited reviewer.

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

- The date when the IRB determined that the criteria for approval were satisfied (i.e., the "approval date");
- The date when verification was made that all IRB conditions have been satisfied (i.e., the “effective date”), and;
- For initial approval and continuing reviews, the date by which continuing review must occur.
**Partial Approval.** The IRB may stipulate that certain components of the research, which the IRB has determined to meet the criteria for approval, may commence or continue while other components of the research that require modification or clarification cannot begin or continue until the outstanding issues are resolved and approved by the convened IRB. For example, the IRB could determine that a study may begin but that children cannot be enrolled until the investigator submits, and the IRB approves, a plan for assent.

**Deferral.** This action is taken by the convened IRB when modifications are required (of the nature or amount that the full IRB cannot make or specify exact changes or parameters), or additional information or clarification is needed in order to determine that one or more criteria for approval are satisfied (e.g., the risks and benefits cannot be assessed with the information provided).

The deferral and the basis for the deferral is documented in the IRB minutes and is communicated to the investigator in writing.

When the convened IRB defers approval, the responsive materials from the investigator will be provided to the convened IRB for review at a subsequent meeting. When the full board defers approval, the original full board reviewer will review the response materials whenever possible. In the event that the original reviewer is unavailable at the meeting during which the submission is being reviewed, the response will be reviewed by the IRB Chair or other qualified IRB member who has been designated to conduct the review.

**Disapproved.** The IRB may determine that the proposed research cannot be conducted at the UNC-Chapel Hill or by employees or agents of UNC-Chapel Hill or otherwise under the auspices of the UNC-Chapel Hill.

Disapproval can only be decided at the convened IRB meeting. An expedited reviewer cannot disapprove a study.

**Approval in Principle.** As per federal regulations, [45CFR46.118], there are circumstances in which a sponsoring agency may require certification of IRB approval as a condition of submitting for or releasing funds but before definitive plans for the involvement of human subjects have been developed (e.g., certain training grants or grants in which the procedures involving human subjects are dependent on the completion of animal studies or instrument development). In these circumstances, the IRB may grant “approval in principle” without having reviewed the as yet undeveloped procedures or materials. The IRB Chair or designee will review the available information (i.e., the grant or proposal and any supplemental information provided by the investigator) and, if appropriate, will provide certification of IRB approval in principal. The investigator must obtain IRB approval before conducting human subjects research.

### 2.6 Continuing Review

The IRB will conduct a continuing review of ongoing research at intervals that are appropriate to the level of risk for each research plan, but not less than once per year. The date by which continuing review must occur will be recorded in the IRB minutes or other IRB records and communicated in writing to the investigator. Continuing review must occur as long as the...
research remains active including when the remaining research activities are limited to the analysis of private identifiable information.

2.6.1 Continuing Review Process

As a courtesy to investigators, the OHRE staff will send out renewal notices to investigators at 60 and 30 days in advance of the expiration date; however, it is the investigator’s responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date. By federal regulation, no extension to that date can be granted.

Investigators must submit the following for continuing review:

1. The initial study application form updated with any changes;
2. The current protocol/research plan;
3. The current consent document;
4. The current Investigator’s Brochure or other updated risk information (if applicable);
5. The most recent report from the DSMB or DMC (if applicable);
6. The most recent multi-center progress report (if applicable);
7. Any proposed modifications to the protocol/research plan, consent, or study; and
8. The progress report (for continuing review).

The complete renewal application can be accessed by all IRB members. Members can request the complete study file (i.e., previous submissions) or any additional materials from the IRB staff prior to the meeting.

In the case of expedited review, the reviewers will have access to the complete study files.

2.6.2 Approval Considerations

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

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

In conducting continuing review of research not eligible for expedited review, all IRB members are provided with access to all of the materials listed in Section 2.6.1 and are responsible for reviewing the project summary, the current consent document, the progress report, and, if applicable, the data and safety monitoring report, multi-center study progress reports, and any proposed modifications to the protocol/research plan, or consent. The Primary Reviewer is responsible for reviewing the complete materials submitted for continuing review including the complete research plan. If requested, the reviewer is given access to the complete IRB file and relevant IRB meeting minutes. At the meeting, the Primary Reviewers assist the Chair in leading the IRB through the completion of the regulatory criteria for approval.

Review of currently approved or newly proposed consent documents must occur during the scheduled continuing review of research by the IRB, but consent documents should be reviewed whenever new information becomes available that may require modification of information in the consent document.

2.6.2.2 Review of PI Responses

The IRB may use the expedited review procedure to approve an investigator’s response to a convened board’s request for minor changes following initial or continuing review of an IRB protocol.

Changes regarded as minor:

- Specific revisions stipulated by the IRB requiring only simple concurrence by the investigator
- Requests for additional information that is not relevant to the IRB’s determination of whether the research meets the regulatory criteria for approval. If the investigator’s response is concordant with the stipulations, or the additional information is provided as requested, the IRB Chair/designee may approve the revised protocol on behalf of the convened board using the expedited review procedure. This action is permitted when the IRB requires modifications (stipulated in the meeting) to secure approval.

Examples of board actions permitting review of the investigator’s response using the expedited procedure:

- If the submission does not include an adequate plan for monitoring the data to ensure the safety of subjects, the board determines what level of monitoring is appropriate and requires the investigator to incorporate the stipulated plan into the protocol.

- Although there might be some ambiguity in the protocol regarding the age range of subjects to be enrolled, the board determines that one or more age ranges would meet the regulatory requirements for approval. The investigator is asked to specify which will be the criterion for eligibility, and if the choice fits within the IRB’s predetermined acceptable range, the protocol may be approved using the expedited review procedure.
• Although it is unclear whether results of genetic testing will be returned to subjects, rather than asking the investigator to clarify, the board determines whether results should be returned and the investigator is asked to concur with the board’s decision.

• To further minimize the risk to individual participants, the board requires that those with known history of a particular condition, for example known heart disease, be excluded from participation.

• To assist in the future review of a protocol, the IRB asks the investigator to add specific information from the sponsor’s protocol to the IRB protocol summary.

Changes that are NOT minor and that may not be expedited by the Chair:

• When the IRB asks substantive questions about the protocol/consent form or requests additional information that is directly relevant to the IRB’s determination of whether the research meets the regulatory criteria for approval (45 CFR 46.111 or 21 CFR 56.111), then approval of the proposed research must be deferred, pending subsequent review of the investigator’s response by the IRB at a convened meeting.

• When the investigator refuses to make modifications stipulated by the convened board, the Chair cannot approve the protocol. The modifications proposed by the investigator, and his justification for not making the IRB’s changes, must be reviewed by the convened IRB for approval for disapproval.

Other examples of board actions requiring review of the investigator’s response by the convened board:

• Request for additional information on pre-clinical or clinical experience with the drug/device/biologic. This additional information is directly relevant to the board’s determination of whether risks to subjects are reasonable in relation to anticipated benefits.

• Request for justification and rationale for doing research biopsies in healthy volunteers. The response has direct bearing on minimizing risks by using procedures that do not unnecessarily expose subjects to risk.

Review of Investigator responses:

• Investigator responses for studies that were reviewed via expedited review will be reviewed by an experienced IRB member; typically the same individual who completed the initial review.

• Investigator responses for studies that were reviewed by the convened IRB and received contingent approval, will be reviewed by the Chair or other experienced expedited reviewer or, upon request, by committee member reviewer(s).

• Investigator responses for studies that were reviewed by the convened IRB and were either deferred or disapproved, will be reviewed by the convened IRB.
2.6.2.3 Expedited Review

In conducting continuing review under expedited procedures, the reviewers will have access to entire study file. The review(s) determine whether the research meets the criteria allowing continuing review using the expedited procedure, and if so, whether the research continues to meet the regulatory criteria for approval.

Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9) (see Expedited Review Categories in Section 2.1.1). It is also possible that research activities that previously qualified for expedited review, have changed or will change, such that expedited IRB review would no longer be permitted for continuing review.

2.6.3 Possible IRB Actions after Continuing Review

As with Initial Review, at the time of Continuing Review, the Convened IRB or IRB Member(s) conducting expedited review may take any of the following actions (see Section 2.5 for a detailed description of these actions):

1. Approval
2. Conditions Required for Approval (i.e., Approval with stipulations)
3. Deferred

Additionally, the convened IRB may vote to disapprove the study. If an IRB member conducting expedited review believes that the study should be disapproved, it will be referred to the convened board for review. If the IRB has significant concerns, the IRB may vote to suspend or terminate the research (See SOP 1402 for a detailed discussion of suspensions and terminations).

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

2.6.4 Lapses in Continuing Review

The regulations permit no grace period or approval extension after approval expiration. Research that continues after the approval period has expired is research conducted without
IRB approval. If re-approval does not occur within the time set by the IRB, all research activities must stop, including recruitment (media advertisements must be withdrawn), enrollment, consent, interventions, interactions, and data collection. This will occur even if the investigator has provided the continuing information before the expiration date. Therefore, investigators must submit their continuing review materials enough in advance of expiration to allow sufficient time for IRB review before the expiration date.

The lapse of IRB approval due to a failure to complete continuing review and obtain re-approval prior to expiration of the prior approval does not ordinarily constitute a suspension or termination of IRB approval, for federal reporting purposes; however, the failure to meet continuing review obligations may be grounds for suspension or termination of the research. If the IRB notes a pattern of non-compliance with the requirements for continuing review (e.g., an investigator repeatedly or deliberately neglects to submit materials for continuing review in a timely fashion), the IRB should determine the reasons for the non-compliance and take appropriate corrective actions. The IRB must report to FDA/OHRP any instance of serious or continuing non-compliance with FDA regulations or IRB requirements or determinations.

The OHRE is responsible for notifying the investigator of the expiration of approval and that all research activities must stop.

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

### 2.7 Modification of an Approved Protocol

Investigators may wish to modify or amend their approved applications. Investigators must seek IRB approval before making any changes, no matter how minor, in approved research -
even though the changes are planned for the period for which IRB approval has already been given - unless the change is necessary to eliminate an immediate hazards to the subject (in which case the IRB must then be notified at once). Changes in approved research that are initiated without IRB approval to eliminate apparent immediate hazards to the participant should be reported to the IRB within 30 days. The changes are reviewed by the IRB to determine whether the changes(s) was consistent with ensuring the participants’ continued welfare.

Modifications may be permanent (Protocol Modification) which make changes to the protocol for all remaining subjects or temporary (Protocol Exceptions) circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient(s)/subject(s) (examples: patient/subject is allergic to one of the medications provided as supportive care; patient/subject is not eligible in a direct benefit study). Usually an Exception is a change that is planned and has prior agreement from the sponsor. See Section 2.7.3 for details on Protocol Exceptions.

Note: Protocol Deviations [see SOP 1401] are unplanned and are reported to the IRB after the fact.

Investigators should consider whether the proposed changes to the research alter the original scope, purpose, or intent of the research. When the research itself is fundamentally changed, the IRB will typically require a new study application rather than allow such changes to be made through a modification to the existing research plan.

### 2.7.1 Modification Procedures

Investigators must submit a modification request to inform the IRB about the proposed changes to the study, including, but necessarily limited to:

- For Protocol Modifications, a revised protocol/research plan, application, and/or study materials (with a detailed summary of changes and the locations of those changes);
- Revised consent/parental permission/assent documents (if applicable);
- When the proposed change(s) to the research might relate to current subjects' willingness to continue to participate in the study and they won't be asked to re-consent using the revised consent form, an information sheet, letter, script, or other mechanism of providing information; and
- Any other relevant documentation provided by the sponsor or coordinating center.

The IRB reviewer will review the submission and make an initial determination whether the proposed changes may be approved through an expedited review process, if the changes are minor, or whether the modification warrants convened board review. The reviewer(s) using the expedited procedure has the ultimate responsibility to determine that the proposed changes may be approved through the expedited review procedure and, if not, must refer the research study for convened board review.
2.7.1.1 Convened Board Review of Modifications

When a proposed change in a research study is not minor, then the IRB must review and approve the proposed change at a convened meeting before the change can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB should be promptly informed of the change following its implementation and should review the change to determine that it is consistent with ensuring the subjects' continued welfare.

All IRB members are provided and review all documents provided by the investigator. At the meeting, the Primary Reviewer presents an overview of the proposed modifications and assists the IRB Chair in leading the IRB through the completion of the regulatory criteria for approval. The IRB will also determine whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

When the IRB reviews modifications to previously approved research, the IRB considers whether information about those modifications might relate to participants’ willingness to continue to take part in the research and if so, whether to provide that information to future/current/past participants.

2.7.1.2 Expedited review of Modifications

An IRB may use expedited review procedures to review minor changes in ongoing previously-approved research during the period for which approval is authorized. An expedited review may be carried out by the IRB Chair and/or experienced designee(s) among the IRB members. The Chair or designee reviews the submission to determine whether the modifications meet the criteria allowing review using the expedited procedure, and if so, whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

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

2.7.2 Possible IRB Actions after Modification Review

As with Initial Review, at the time of Continuing Review, the Convened IRB or IRB Member(s) conducting expedited review may take any of the following actions (see Section 2.5 for a detailed description of these actions):

1. Approval
2. Conditions required for Approval
3. Deferred

Additionally, the convened IRB may vote to disapprove the proposed changes. If an IRB member conducting expedited review believes that the proposed modifications should be disapproved, they will refer the proposed modification to the convened board for review. If the
proposed changes raise significant concerns on the part of the IRB, the IRB may vote to suspend or terminate the research (See SOP 1402 for a detailed discussion of suspensions and terminations).

2.7.3 Protocol Exceptions

A Protocol Exception is a type of planned change to the research. Unlike an amendment, a protocol exception is not a permanent revision to the research protocol. A Protocol Exception may be permitted:

- For an individual subject (i.e., Single Subject Protocol Exception) when it is in the best interest of that subject and the subject does not meet the current approved Inclusion/Exclusion (I/E) criteria.
- When IRB approval has lapsed (or is expected to lapse) and the investigator wishes to continue research interventions or interactions for some or all subjects when it is in the best interest of the subjects to continue.

A Protocol Exception must not adversely affect the safety of the subject(s) or integrity of the study data. Similar to an amendment or modification, the PI is responsible for submitting any protocol exceptions prior to initiation of the change to the IRB. Failure to submit all protocol exceptions represents non-compliance with the federal regulations and UNC policies.

2.7.3.1 Single Subject Protocol Exception

A Single Subject Protocol Exception should be rare, is limited to a single subject and justified in terms of serving the best interests of the potential study participant. The inclusion of additional participants who do not meet the eligibility criteria requires an amendment (i.e., modification) to the protocol.

If the research involves an investigational agent (drug, device, or biologic), prior approval by the sponsor is also required. Additionally, when the research involves an investigational device and the changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of the subjects, FDA pre-approval is required [21 CFR 812.150 (4)].

If the research is investigator-initiated, a colleague uninvolved in the care of the subject must provide a written endorsement for the inclusion of the ineligible person because alternatives are limited to less favorable options.

2.7.3.1.1 Requesting a Protocol Exception

The Investigator will submit a modification requesting a Protocol Exception. Protocol Exceptions should be submitted separately from other modification requests. A Protocol Exception Request Form must be completed and submitted along with any additional required documentation. The investigator must explain the underlying reasons for which the protocol exception is requested and where an over-riding safety concern or ethical issue indicates that it is in the best interest of the individual to continue participating.
If a protocol exception request cannot be submitted via IRBIS because a previous submission is under review, the investigator should call the IRB (919-966-3113) and inform the receptionist that you have a protocol exception that cannot be submitted via IRBIS due to a pending review. The receptionist will refer you to an IRB Analyst who will guide you through the submission process.

Investigators are encouraged to submit all single subject protocol exception requests as soon as the potential subject is identified. If the request is time-sensitive, the investigator should be sure to indicate this when calling the IRB office, or, if applicable, handle as Emergency Use (described below.)

2.7.3.1.2 Alternatives to a Single Subject Protocol Exception

A Single Subject Protocol Exception should be rare, and is generally limited to a single subject. Subsequent requests may be denied. The following alternatives should be considered.

Off protocol – If the treatment being studied under this protocol is FDA-approved, the patient may be treated off protocol.

Protocol Amendment -- Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, inclusion/exclusion criteria, study design, sample sizes, study procedures, or significant administrative aspects.

Expanded Access to Investigational Drugs for Treatment Use (Compassionate Use) --The purpose of an expanded access protocol is to make investigational drugs available to patients who do not qualify for participation in a clinical trial. Expanded access protocols allow a larger group of people to be treated with the drug.

Emergency Use is defined as the use of an investigational drug, biologic or device with 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. The emergency use exemption is permitted only if each of the following conditions exists as outlined in 21 CFR 56.102(d). 1) A life-threatening or severely debilitating situation exists necessitating the use of the investigational drug, biologic or device; 2) No standard acceptable alternative treatment is available; and 3) Because of the immediate need to use the drug, biologic or device, there is not sufficient time to use existing procedures to obtain IRB approval for the use.

2.7.3.2 Protocol Exception to Conduct Research During Approval Lapse

Request for approval during approval lapse should be rare. The expectation is that researchers will submit renewal applications well in advance of the expiration date however; there may be circumstances that result in an unexpected IRB approval lapse. In these cases, the investigator may submit a request for a protocol exception to conduct research during approval lapse when it is in the best interest of the subjects to continue.
2.7.3.2.1 Requesting a Protocol Exception to Conduct Research during Approval Lapse

Interventions are allowed to continue only when it is in the best interest of the subjects and when approved by the IRB. To request the continuation of certain aspects of the research, the investigator must submit a Protocol Exception Request Form describing the activities. The investigator must also explain the underlying reasons for which the protocol exception is requested for each activity and each subject. A protocol exception must be requested even if a continuing review application has been submitted. Approval of a protocol exception does not replace or represent continuing IRB review of the research.

The Investigator should first call the OHRE and request to speak with an IRB Analyst. The Protocol Exception Request Form should be completed and emailed directly to the IRB Analyst. Once the protocol exception has been reviewed, the IRB will return the form, which has been completed by the IRB, to the Investigator (or designee) via e-mail. Following continuing review and approval of the study, the Investigator will submit a modification via IRBIS. The modification should include a completed copy of the Protocol Exception Request Form on which the IRB decision has been documented. Doing so will document the protocol exception approval in IRBIS.

2.7.3.3 IRB Review of Protocol Exceptions

1. The Protocol Exception Form will be reviewed to determine if the request represents no greater than minimal risk and is limited to minor changes in previously approved research. The Chair (or designee) will review the request and evaluate the impact of the protocol exception with regards to:
   a. The safety of the research participant
   b. The potential benefits to the subject
   c. Affect to the rights or welfare of the subject
   d. Integrity of the data

2. If the protocol exception represents changes that are no greater than minimal risk and is limited to minor changes, the Chair or designee may review the request via Expedited Review as described in §46.110(b). A summary of the review will be documented in the study submission notes.

3. If the reviewer determines that the Protocol Exception request represents changes that are greater than minimal risk and/or more than minor changes, or is otherwise not approvable, the Protocol Exception should be placed on the next available Full Board agenda. A summary of the review will be documented in the Internal Meeting Notes.

Lapse in IRB approval represents non-compliance. If the Chair or designee determines that the lapse represents possible continuing noncompliance, it is referred to the Safety Committee for a final determination.
Examples of Single Subject Protocol Exceptions that require Full Board Review

A dose increase of the investigational drug dose that is not allowed by the current approved protocol.

Request to enroll a potential subject who is currently taking an excluded medication.

Examples of Single Subject Protocol Exceptions that may be reviewed by Expedited Review

The protocol requires PET scan for tumor imaging within 28 days of being enrolled into the study. The potential subject’s last PET scan was completed 32 days ago (i.e., 4 days out of window). The Investigator does not believe that a repeat CT scan is in the best interest of the subject.

Subject ID 003 experienced an infusion rate reaction during the third dose of the investigational drug. The patient was re-challenged at a slower rate of infusion and successfully completed treatment without further reaction. The Investigator is requesting that use of a slower infusion rate for this subject for all subsequent doses.

Subject ID 024 requires a 60 day (+/- 7 days) follow-up visit. The subject will be traveling during this time and is not available to come in for the visit until January 5th which is 7 days out of window. (Note: The IRB will consider the number of days outside of window and potential risk to the subject.)

Examples of Requests that should not be submitted as Protocol Exceptions

Request for approval to complete screening visits during lapse of approval because subjects have already been scheduled.

2.8 Closure of Research Studies

The completion or early termination of the study, is a change in activity and must be reported to the IRB. Although subjects will no longer be "at risk" under the study, a final report to the IRB allows it to close its files as well as providing information that may be used by the IRB in the evaluation and approval of related studies.

Studies may be closed when the involvement of human subjects ceases (interventions, interactions, observations, and the gathering, use, study, and analysis of identifiable private information, including specimens, are all complete). Studies may be closed when the only remaining research activity involves the analysis of unidentifiable individual level data, or aggregate data sets.

For multi-center research, the study may be closed once all research activities (as above) are complete at the UNC-Chapel Hill and any sites for which the IRB is the “IRB of record”. If the investigator is serving as the lead investigator or the UNC-Chapel Hill is the coordinating center, please note that the study must remain open as long as the coordinating center is still receiving, studying, using, or analyzing identifiable private information from other sites (even if local interventions, interactions, observations, and data gathering is complete).

Investigators may submit study closures to the IRB via IRBIS. With closure submissions, the investigator must also complete the progress report questions.

The IRB reviewer will confirm the disposition of the data and/or specimens that they collected, including identifiable private data, is consistent with the IRB-approved research plan. Investigators may not conduct any additional analysis of identified data without re-applying for IRB approval. Investigators must continue to protect the confidentiality of the data as
described to the IRB and honor any other commitments that were agreed to as part of the approved research including, for example, future use of data or specimens, provision of research results to subjects, and provision of any outstanding payments or compensation.

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

2.9 Reporting IRB Actions

All IRB actions are communicated to the investigator, and/or designated contact person(s) for the research study, in writing via an electronic template letter. For an approval, along with written notification of approval, access to the approved consent/assent/permission form/s (if applicable) will be provided to the investigator. For approval with conditions, the notification will include a listing of the conditions that must be satisfied. For a deferral, the notification will include the modifications and/or clarifications required along with the basis for requiring those modifications. For a disapproval, termination or suspension, the notification will include the basis for making that decision and give the investigator an opportunity to respond in person or in writing.

All research documents are maintained by the IRB for a period of up to three years following closure of the study.

The IRB reports its findings and actions to the organization in the form of its minutes, which are distributed by IRB staff to the UNC-Chapel Hill Institutional Official.

2.10 Failure to Respond

Failure to submit a response to IRB requirements within 90 days of the IRB date of determination may result in administrative closure of the IRB file (for new study submissions). When research has IRB approval, and an investigator fails to respond to requirements related to a subsequent submission (e.g., a request for modification), the IRB reviewer will review the circumstances, including any potential impact on human subjects, and will contact the investigator to try to secure a response. If the investigator continues to be unresponsive, the failure of the investigator may be considered non-compliance and may be reviewed in accordance with the procedures in SOP 1402. The investigator will receive notification, including an explanation. An extension beyond 90 days may be granted by the IRB if sufficient cause is provided by the investigator.

2.11 Appeal of IRB Decisions

When an IRB research study is disapproved or deferred, the IRB will notify the investigator in writing about the specific deficiencies and the modifications that are necessary for appropriate IRB approval. The IRB shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. Similarly, when research is suspended in part or in full, or terminated, the IRB will notify the investigator in writing of the suspension or termination and the reasons for its decision. The investigator
may ask that the decision be reconsidered by submitting a request in writing to the IRB. The request must contain the basis for the appeal, including any substantive new information that the Board did not have the opportunity to consider previously. The request is scheduled for review at a convened IRB meeting; at the discretion of the Chair, the Investigator may invited to attend the meeting.

2.12 Research Previously Approved By Another IRB

When an investigator transfers research to the UNC-Chapel Hill that was previously approved by another IRB, the investigator must submit the research for review under the procedures covered by this section. No research activity may take place under the UNC-Chapel Hill auspices without the appropriate review and approval.

Research approved as exempt at the previous institution will be reviewed according to the procedures in SOP 601. All other research must be submitted as if it were undergoing initial review and will be reviewed under expedited review or by the convened IRB. Research that solely involves the analysis of existing identifiable data may be considered under Expedited Review Category 5.

For research transfers where stopping research interventions might harm subjects, the investigator can request permission from the IRB to continue research interventions under the oversight of the prior organization’s IRB until final the UNC-Chapel Hill approval is obtained.

3 Definitions

**Minimal Risk.** Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

**Minor Change.** A minor change is one which, in the judgment of the IRB reviewer, makes no substantial alteration in:

1. The acceptability of the risk-to-benefit analysis or increases the level of risks to subjects
2. The research design or methods (adding procedures that are not eligible for expedited review (See Section 2.1) would be considered more than a minor change
3. The number of subjects enrolled in the research (usually not greater than 10% of the total requested locally)
4. The qualifications of the research team
5. The facilities available to support safe conduct of the research
6. Any other factor which would warrant review of the proposed changes by the convened IRB
**Quorum.** A quorum of the IRB consists of a majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area. When research involving an investigational new drug is on the agenda for review, a physician should be included in the quorum.

**Suspension of IRB approval.** A suspension of IRB approval is a directive of the IRB to temporarily stop some or all previously approved research activities. Suspended research studies remain open and require continuing review. Investigators must continue to provide reports on adverse events and unanticipated problems to both the IRB and sponsors just as if there had never been a suspension (i.e., all events that need to be reported during a study need to continue to be reported during the suspension period). If a suspension is lifted and IRB approval of the suspended research study has expired, a continuing review is required before the study may resume.

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

An “Institutional-, investigator- or sponsor-initiated hold” refers to a voluntary action by the institution, investigator or sponsor of the study to place some or all research activities associated with that study on hold. Institutional, investigator or sponsor holds may be the result of interim data analysis, inadequate drug availability, response to a DSMB report/recommendation, pre-planned stopping point or other information. An institutional-, investigator-, or sponsor-initiated hold is not a suspension or termination of IRB approval; therefore a study placed on “hold” is (i) subject to continuing review by the IRB; and (ii) not subject to reporting requirements as defined in SOP 1402, Management of New Safety Information.

An institutional, investigator or sponsor hold should be reported to the IRB as new safety information in accordance with SOP 1401, Reporting New Safety Information if the hold is a result of safety concerns. All other institutional, investigator or sponsor holds should be submitted as modifications to previously approved research.

2 Procedures

1. The submission should include the following information:
   a. Describe the basis for the hold
   b. Describe the research activities that will be halted. Research activities may include but are not limited to recruitment, screening/enrollment, research intervention/interaction, and follow-up.
   c. If applicable, describe actions implemented prior to submission, in order to eliminate apparent immediate harm to subjects
   d. Provide a plan for how to notify research participants of the hold.
   e. Describe conditions that must be satisfied in order to lift the hold.

2. A Chair or the Safety Welfare Analysis Committee (SWAG) will review the institutional-, investigator-, or sponsor-initiated hold and may do any of the following:
   a. Approve the hold
   b. Request additional changes or information
c. Refer the study for review by the convened IRB

d. Suspend IRB approval and refer the study for review by the convened IRB

3. When a study or a part of a study is placed on hold by the institution, the investigator or the sponsor may not resume until the investigator submits and the IRB approves a modification or a new safety information follow-up report to lift the hold. If, in addition to the hold, IRB approval is suspended, research activities may not resume until the processes outlined in SOP 1402, Management of New Safety Information are followed.

3. Definitions

An “Institutional, investigator or sponsor hold” refers to a voluntary action by the institution, investigator or sponsor of the study to place some or all research activities associated with that study on hold.
1 Purpose

All non-exempt human subject research conducted under the auspices of the UNC-Chapel Hill must be reviewed and approved by the UNC Chapel Hill IRB or another designated IRB prior to the initiation of the research unless it has been determined that UNC-Chapel Hill is not engaged in the research. The authorized off-site IRBs that serve as the IRB-of-record for UNC-Chapel Hill have the same authority as the on-site IRBs and all determinations and findings of the off-site IRBs are equally binding on all research under the auspices of the organization.

In the conduct of cooperative research projects, UNC-Chapel Hill acknowledges that each organization is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations. It is the policy of UNC-Chapel Hill to assure that all facilities participating in a study involving human subjects receive adequate documentation about the study in order to protect the safety, welfare and interests of study participants.

2 Procedure

2.1 Commercial IRB

The University of North Carolina at Chapel Hill (UNC-Chapel Hill) requires the use of a pre-approved Commercial IRB for industry-sponsored, multi-center, clinical research studies as outlined in SOP 401.

Investigator-initiated studies are only eligible for review by Commercial IRBs; at the discretion of the OHRE Director or Reliance Leadership.

2.1.1 Investigator Responsibilities

1. Prior to submitting the application package to the external IRB, the investigator must satisfy the UNC-Chapel Hill application requirements for externally reviewed studies. An abbreviated IRBIS application must be completed in order for the UNC Chapel Hill IRB to confirm completion of all institutional requirements (e.g., radiation safety, COI disclosure, applicable training, data security) and for record-keeping purposes.

2. Per our agreements with the Commercial IRBs, the Commercial IRB will invoice the Sponsor/CRO directly. UNC charges an additional preparation/processing fee which should be included in the study budget.
3. The UNC-Chapel Hill Responsibilities Prior to Accepting External Oversight for a Study

Following submission of the abbreviated application in IRBIS, the IRB reviews the following:

- Review application for completeness and consistency between sections
- Eligibility to use external IRB review (industry-sponsored)
- Review of investigator and study staff (confirmation of training and COI disclosure)
- Review of Institutional requirements (e.g., radiation safety, Investigational Drug Services (IDS) pharmacy)
- As privacy board: If applicable, adequacy of justification for limited waiver of HIPAA and if HIPAA Authorization form if free-standing (i.e., not embedded into the main consent document) is reviewed for required content.

Once the above are reviewed by the IRB and determined to be acceptable, the IRB issues the investigator a Permission to Register/contingency letter and UNC-Chapel Hill study specific Cover Sheet. The letter permits the investigator to move forward with their submission to the external IRB, while the Cover Sheet provides applicable study specific information, e.g., stand-alone HIPAA authorization information, IRBIS number, sites and results of ancillary reviews including COI disclosure (managed by the Conflict of Interest Office), Radiation Safety Committee, and subject injury language concurrence with the clinical trial agreement [CTA](managed by the Clinical Trials Office). Both COI disclosure and subject injury language for Network Entity researchers is managed by the Network Entities Research Compliance office.

2.1.2 The UNC-Chapel Hill Responsibilities: Post Commercial IRB Approval

Once the investigator has submitted the study to the Commercial IRB along with the Cover Sheet signifying the UNC OHRE sign-off and has received approval from the Commercial IRB, the following will be reviewed as part of routine auditing:

- Review of the Commercial IRB-approved consent document:
  - Confirm congruency of institutional specific requirements stated in the Cover Sheet and UNC specific ancillary review documentation.

Investigators approved through Commercial IRB review must still report local unanticipated problems, complaints, non-compliance, and an annual and end of study summary to the UNC-Chapel Hill IRB Office in addition to any external IRB reporting requirements. The addition of study personnel must be submitted to the UNC-Chapel Hill IRB prior to the personnel assuming any study responsibilities.

The Commercial IRB must copy the IRB Office on all determinations of continuing or serious non-compliance and unanticipated problems involving subjects or others (UPIRSO). These will be reviewed by the UNC-Chapel Hill IRB Compliance Office.

The investigator must “renew” the study with the UNC IRB by completing an abbreviated renewal submission that includes submission of the current approved consent forms and
current external IRB approval letter. As with all studies, COI disclosure must be completed at least annually by applicable members of the research team.

2.2 National Cancer Institute’s Central IRB Adult and Pediatrics Initiative

The UNC-Chapel Hill is a participant in the National Cancer Institute’s Central Institutional Review Board (CIRB) Initiative for cooperative group protocols/studies that have been reviewed and approved by the CIRB. The UNC-Chapel Hill IO (or designee) submits the necessary documentation to maintain institutional registration with the CIRB, including the “Authorization Agreement/Division of Responsibilities”, the listing of Key Personnel, and the “Annual Signatory Institution Worksheet About Local Context”.

The CIRB defers responsibility to local institutions to conduct any reviews necessary under HIPAA. The CIRB does accept institutional boilerplate language for HIPAA authorizations if an institution incorporates authorization into the consent document.

UNC-Chapel Hill uses free-standing HIPAA authorizations for research; investigators should use the standard authorization form. Requests for a limited HIPAA wavier for use of PHI to identify and/or screen potential candidates should be submitted to the UNC IRB via IRBIS. The Lineberger Comprehensive Cancer Center (LCCC) NCI CIRB manager Office will include HIPAA authorization language when it submits the “Annual Signatory Institution Worksheet About Local Context”.

The CIRB relies on local institutions to identify potential conflicts of interest and to develop conflict management plans. The UNC-Chapel Hill investigators should submit disclosures to the UNC Conflict of Interest office. Investigators must submit conflict management plans for themselves or members of the local research team to the CIRB using the “Study-Specific Worksheet About Local Context”.

Investigators wishing to use the NCI CIRB must:

1. Contact the Lineberger Comprehensive Cancer Center (LCCC) NCI CIRB manager to request the materials necessary to register as an investigator with the CIRB.

2. Complete, on an annual basis, the “Annual Principal Investigator Worksheet About Local Context” and submit to the LCCC NCI CIRB manager and to the CIRB. Once CIRB-approved, the investigator may proceed with individual study applications.

3. In order to open individual protocols/studies under the CIRB, the investigator submits an application to the UNC-Chapel Hill IRB via IRBIS that includes the following:
   
a. Study Summary and Key Personnel,
   b. Abbreviated IRB application,
   c. The protocol/research plan version, investigator brochure(s), and model consent currently approved by the NCI CIRB,
   d. The consent form for local use with required local institutional language incorporated,
e. Translations of the consent form for local use with accompanying translation verification form,
f. CITI Training is documented electronically for each member of the research team,
g. Conflict of Interest disclosure is completed for applicable members of the research team, and
h. The application is signed electronically by the principal investigator and department signatories.

4. The UNC-Chapel Hill IRB Office will review the abbreviated application, facilitate the COI review process, and provide a letter either accepting or declining CIRB oversight of the study (as a component of organizational approval).
   a. If accepted, the investigator may then proceed with the application to the CIRB by submitting the CIRB “Study-Specific Worksheet About Local Context”. Note: If a member of the research team has a COI Management Plan, this must be submitted to the CIRB.
   b. If declined, a reason will be provided and the investigator will be given an opportunity to provide additional or clarifying information. In the event that the decision to decline is confirmed on re-review, the investigator may appeal the decision by contacting the IRB office.

5. Once approved by the CIRB, a copy of the CIRB approval must be submitted to the UNC-Chapel Hill IRB Office via IRBIS.

Ongoing responsibilities after study approval:

1. The UNC-Chapel Hill is responsible per written agreement with the CIRB to ensure compliance with the regulations governing research and the determinations made by the CIRB, and to report possible serious or continuing non-compliance and unanticipated problems to the CIRB for evaluation. In order to fulfill these responsibilities. The UNC-Chapel Hill needs to maintain current documentation of the study, the actions taken by the CIRB, and any local issues that arise with the research. At least annually, the investigator will need to submit the following to the IRB office:
   a. Amended protocols/research plans, investigator brochure(s), model and local consents, translated consents, and the associated documentation of CIRB approval;
   b. Audit reports;
   c. Local unanticipated events, protocol/research plan exceptions, and protocol/research plan deviations;
   d. Local subject complaints or unresolved concerns;
   e. Changes in local study personnel;
   f. Changes in study status locally and study-wide (Open to Enrollment, Closed to Enrollment, Suspended, etc.);
g. Conflict of Interest disclosures on an annual basis or within 30 days of a change in significant financial interests or circumstances that could represent a conflict of commitment;

h. Current training records (CITI or accepted alternative) for each member of the local research team; and

i. An annual summary of study activity describing the number of local enrollees and status of enrollees (screen failure, on treatment, on follow up, withdrawn, complete, deceased), the study status (open to enrollment, closed to enrollment – active treatment, closed to enrollment – follow up only, closed to enrollment – data analysis, all local activities complete (closed)), any shifts in the evidence or in standard care that could impact the target study population or enrollment into the study, and any local complaints, concerns, or problems with the research.

2. The UNC-Chapel Hill IRB Office staff will review submissions and seek additional information, if needed, from the local research team. The UNC-Chapel Hill IRB Office will report potential unanticipated problems, potential serious or continuing non-compliance, local suspensions or terminations of research activities, and audit reports that note regulatory deficiencies to the CIRB. The report will include, if applicable, a corrective and preventative action plan (CAPA) developed in cooperation with the investigator. The CIRB will make a final determination regarding whether or not such events are unanticipated problems involving risks to subjects or others, serious non-compliance, or continuing non-compliance and will initiate any necessary reporting to sponsors and federal agencies.

3. Local investigators are responsible for submitting any COI management plans, translated consent forms (with accompanying certificate of translation), local subject materials, and local advertisements and recruitment materials to the CIRB.

4. Research open under the CIRB remains subject to the UNC-Chapel Hill and HRPP policies and procedures including, but not limited to, internal and external audits, training requirements, advertisements, privacy, and confidentiality.

2.3 Investigator-Initiated Collaborative Research

When employees or agents of the applicable UNC-CH conduct investigator-initiated non-exempt human-subjects research in collaboration with other institutions or with collaborating individual investigators as defined herein, each collaborating institution and/or collaborating individual investigator engaged in human-subjects research must obtain IRB approval for the research they are conducting. The OHRP guidance document Guidance on Engagement of Institutions in Human Subjects Research will be used as the basis for determining engagement in human-subjects research. Such determinations will be made by UNC IRB in collaboration and consultation with authorized representatives of the collaborating institution and/or the collaborating individual investigators, as applicable.

Investigators must specify in the UNC-CH IRB application the outside institutions and/or individuals involved in the research. Additional information required in the application is specified in OHRE’s guidance document How to Request a Reliance Agreement.
2.3.1 Collaborating Institutions

Per relevant guidance from OHRP, when multiple institutions are engaged in the same non-exempt human-subjects research, the collaborating institutions may enter into joint review arrangements, rely upon the review of another qualified IRB, or make similar arrangements to avoid duplication of effort. When an institution is engaged in only part of the non-exempt human-subjects research, the institution must ensure that the part of the research project in which the institution is engaged is reviewed and approved by the institution’s IRB or, on behalf of the institution, by another appropriately qualified IRB or Ethics Committee (EC). Alternatively, each institution may decide to review the entire research project, even if the information about the entire project is not necessary to approve the part(s) of the research in which the institution is engaged.

2.3.1.1 Reliance of Collaborating Institutions on the UNC-CH IRB

Collaborating institutions engaged in non-exempt human-subjects research may request to rely on the UNC-CH for review of the research. In such cases, the UNC-CH IRB will consider the request and, if it is granted, an IRB Authorization Agreement (IAA) also referred to as a Reliance Agreement must be executed by both institutions. The relying institution must have an active/approved FWA. In the absence of such a reliance arrangement, each institution will independently review the research project.

2.3.1.2 Reliance of the UNC-CH IRB on Collaborating Institution’s IRB

UNC-CH may rely on the IRB of a collaborating institution. This may be because the majority of the non-exempt human-subjects research is being conducted at the collaborating institution, the collaborating institution’s IRB has more relevant or specialized expertise and/or knowledge of the site where the research will be conducted, or because the collaborating institution has been designated as the sIRB (single IRB). In such cases, an IAA must be executed by both institutions. The institution relied upon for IRB review must have an active/approved FWA. In the absence of such a reliance arrangement, each institution will independently review the research project.

2.3.1.3 Joint Review Arrangements

When UNC-CH IRB and the collaborating institution are each engaged in only part of a non-exempt human-subjects research project, each may decide to review only the part(s) of the project in which they are engaged. The UNC-CH IRB will make decisions about appropriate joint review arrangements depending on the circumstances of the particular project.

2.3.2 Collaborating Individual Investigators

When a collaborating individual investigator, whether an independent investigator or an institutional investigator, is engaged in non-exempt human-subjects research, UNC-CH may choose to extend its FWA to cover the collaborating individual investigator. In such cases, an
Individual Investigator Agreement outlining the terms and conditions of this arrangement must be executed by both parties.

2.3.2.1 Disagreements among designated IRBs in multi-center research

The UNC-Chapel Hill IRBs welcome the input of IRBs at different institutions; however, the UNC-Chapel Hill IRB is ultimately responsible for the welfare of subjects at the University and must make decisions accordingly.

In research in which the UNC-Chapel Hill IRB has agreed to rely on another IRB for review of a given study, the UNC-Chapel Hill IRB has the authority to rescind this authorization at any time.
1 Purpose

The University of North Carolina at Chapel Hill (UNC-Chapel Hill) prepares and maintains adequate documentation of the IRB’s activities. All records are accessible for inspection and copying by authorized representatives of the FDA, OHRP, sponsors, and other authorized entities at reasonable times and in a reasonable manner.

2 Procedure

2.1 IRB Operations Records

Records documenting the daily operations of the IRB include, but are not limited to:

1. Written operating procedures
2. IRB membership rosters
3. Training records documenting that investigators, IRB members, and IRB staff have fulfilled the UNC-Chapel Hill’s human subject training requirements
4. IRB correspondence including reports to regulatory agencies
5. Convened IRB meeting minutes
6. Correspondence by the convened IRB
7. Federal Wide Assurances
8. IRB Registrations

2.2 IRB Study Records

The IRB maintains a separate IRB study record for each research application in UNC IRB Information System (IRBIS). IRBIS assigns each research study a unique identification number called an IRB Study number (e.g., 16-0010). Hard copies of study records generated prior to the initiation of IRBIS are archived at UNC’s archival repository.

Accurate records are maintained of all communications to and from the IRB. Copies are uploaded to the study record in IRBIS. The UNC-Chapel Hill IRB study records includes, but is not limited to:

1. Research plan and all other documents submitted as part of a new study application
2. Research plan and all other documents submitted as part of a request for continuing review or closure of research application
3. Documents submitted and reviewed after the study has been approved, including modification requests, protocol/research plan exception requests, proposed advertisements, data and safety monitoring reports, and reports of new safety information
4. Copy of IRB-approved Consent/Assent/Parental Permission Documents
5. DHHS-approved sample consent form document and research plan, when they exist
6. Documentation of scientific or scholarly review (if applicable)
7. Documentation of type of IRB review. For exempt determinations and expedited review, this will include the category under which the review is allowed
8. For expedited review, documentation of any findings and determinations required by the regulations and study-specific findings supporting those determinations, including, but not limited to, waiver or alteration of consent, waiver of documentation of consent, research involving pregnant women, fetuses, and neonates, research involving prisoners, and research involving children. For research reviewed by the convened board these findings and determinations are recorded in the minutes.
9. For expedited review, documentation of the risk determination and period of approval. For research reviewed by the convened board these determinations are recorded in the minutes.
10. Documentation of review by another institution’s IRB when appropriate
11. Documentation of reliance agreements
12. Documentation of complaints and any related findings and/or resolution.
13. Approval letters that include any requirements that the investigator must satisfy before beginning the study
14. Documentation of all IRB review actions
15. Notification of expiration of IRB approval to the investigator and requirements related to the expiration
16. Notification of Suspension or Termination of research
17. Notification of Unanticipated Problem Involving Risk to Subjects or Others.
18. Notification of Continuing Noncompliance and Serious Noncompliance
19. IRB correspondence to and from research investigators
20. All other IRB correspondence related to the research
21. For devices, documentation of determination by IRB of significant risk/non-significant risk
22. Documentation of audits, investigations, reports of external site visits
2.3 The IRB Minutes

Proceedings are written and available for review by the next regularly scheduled IRB meeting. Once accepted by the members, the minutes must not be altered by anyone including a higher organizational authority.

A copy of IRB-approved minutes for each IRB meeting will be distributed to the IO.

Minutes of IRB meetings must contain sufficient detail to show:

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

Note: The attendance list shall include those members present at the beginning of the meeting. The minutes will indicate, by name, those members who are not present for the discussion and vote. The vote on each action will reflect the numbers of members present for the vote on that item. Members who recuse themselves because of conflict of interest are listed by name and the reason documented.

2. The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area.

3. Business Items discussed

4. Continuing education

5. Actions taken, including separate deliberations, actions, and votes for each research study undergoing review by the convened IRB.

6. Vote counts on these actions (Total Number Voting; Number voting for; Number voting against; Number abstaining; Number of those recused)

7. Basis or justification for actions disapproving or requiring changes in research

8. Summary of controverted issues and their resolution
9. Approval period for initial and continuing reviews, including identification of research that warrants review more often than annually and the basis for that determination
10. Risk determination for initial and continuing reviews, and modifications when the modification alters the prior risk determination
11. Justification for deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document.
12. Study-specific findings supporting that the research meets each of the required criteria when approving a consent procedure that does not include or that alters some or all of the required elements of informed consent, or when waiving the requirement to obtain informed consent altogether
13. Study-specific findings supporting that that the research meets each of the required criteria when the requirements for documentation of consent are waived
14. Study-specific findings supporting that the research meets each of the criteria for approval for vulnerable populations under any applicable Subparts.
15. Study-specific findings and required determinations justifying those determinations for research involving subjects with diminished capacity.
16. Significant risk/non-significant risk device determinations and the basis for those determinations.
17. Determinations of conflict of interest and acceptance or modification of conflict management plans.
18. Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research.
19. Review of interim reports, e.g., new safety information; modification requests; etc.
20. An indication that, when an IRB member or alternate has a conflicting interest (see Section 21.2) with the research under review, the IRB member or alternate was not present during the final deliberations or voting.
21. Key information provided by consultants will be documented in the minutes or in a report provided by the consultant.
2.4 IRB Membership Roster

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

1. Name.
2. Earned degrees.
3. Employment or other relationship between each member and the organization (i.e., affiliated or non-affiliated). To be categorized as non-affiliated, neither the member nor an immediate family member of the member may be affiliated with the UNC-Chapel Hill.
4. Status as scientist or non-scientist. Members whose training, background, and occupation would incline them to view scientific activities from the standpoint of someone within a behavioral or biomedical research discipline are considered a scientist for the purposes of the roster, while members whose training, background, and occupation would incline them to view research activities from a standpoint outside of any biomedical or behavioral scientific discipline are considered a nonscientist.
5. Indications of experience, such as board certifications, licenses, and areas of practice sufficient to describe each member's chief anticipated contributions to IRB deliberations.
6. Representative capacities of each IRB member; including which IRB member(s) is a prisoner representative, and which IRB members are knowledgeable about or experienced in working with children, pregnant women, cognitively impaired individuals, and other vulnerable populations commonly involved in the UNC-Chapel Hill research.
7. Role on the IRB (Chair, Vice-Chair, etc.)
8. Voting status
9. For alternate members, the primary member or class of members for whom the member could substitute

The IRB office must keep the IRB membership list current. The OHRE Compliance Manager will report changes in IRB membership to OHRP/FDA within 90 days of the change.

2.5 Documentation of Exemptions

Documentation of verified exemptions consists of the reviewer’s citation of a specific exemption category that the activity described in the investigator’s request for satisfies the conditions of the cited exemption category as detailed in SOP 601.
2.6 Documentation of Expedited Reviews

IRB records for initial and continuing review by the expedited procedure must include: the specific permissible category; that the activity described by the investigator satisfies all of the criteria for approval; the approval period and any determinations required by the regulations including study-specific findings justifying the following determinations:

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

2.7 Access to IRB Records

The IRB has policies and procedures to protect the confidentiality of research information:

1. All IRB records are kept on a secure UNC server or in locked filing cabinets or locked storage rooms. Computers are password protected. Doors to the IRB Offices are closed and locked when the rooms are unattended.
2. Ordinarily, access to all IRB records is limited to the OHRE Director, IRB Chair, IRB members, IRB Managers, IRB Analysts, IRB staff, authorized organizational officials, and officials of federal and state regulatory agencies (e.g., OHRP and FDA). Research investigators are provided reasonable access to files related to their research. Appropriate accreditation bodies are provided access. All other access to IRB records is limited to those who have legitimate need for them, as determined by the IO and the OHRE Director.
3. Records are accessible for inspection and copying by authorized representatives of federal regulatory agencies during regular business hours.
4. Records may not be removed from the IRB Office; however, the IRB staff will provide copies of records for authorized personnel if requested.
5. All other access to IRB study records is prohibited.

2.8 Record Retention and Disposition

The IRB records detailed above shall be retained and disposed of as per the Section 6.4, 6.10 and 6.11 of The University of North Carolina at Chapel Hill General Records Retention and Disposition Schedule.

For records not included in the UNC-CH General Records Retention and Disposition Schedule, refer to Federal retention requirements:
DHHS regulations require that, “records relating to research which is conducted shall be retained for at least 3 years after completion of the research.” [45 CFR 46.115(b)] If a protocol is cancelled without subject enrollment, IRB records are maintained for at least three years after cancellation.

FDA regulations require that sponsors and investigators of an Investigational New Drug (IND) retain “records and reports required by this part for 2 years after a marketing application is approved for the drug; or if an application is not approved for drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA so notified.” [21 CFR 312.57(c)]

FDA regulations require that the investigator or sponsor of an Investigational Device Exemption (IDE) maintain the records “for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.” [21 CFR 812.140(d)]

2.9 Public Records request

Some of this documentation may be subject to public access under the North Carolina Public Records Act and/or the Federal Freedom of Information Act (FOIA). The Office of University Counsel should be consulted when a public records request is received.

3 References

21 CFR 46.115
21 CFR 56.115
21 CFR 312.57(c)
21 CFR 812.140(d)

UNC General Records Retention and Disposition Schedule published April 25, 2016
1  Purpose

No investigator conducting research under the auspices of the University of North Carolina at Chapel Hill (UNC-Chapel Hill) may involve a human being as a subject in research without obtaining the legally effective informed consent of the subject or the subject’s legally authorized representative unless a waiver of consent has been approved by the IRB in accordance with Section 2.9 of these procedures. Except as provided in Sections 2.10 and 2.11 of these procedures, informed consent must be documented by the use of a written consent form approved by the IRB.

The IRB will evaluate both the consent process and the procedures for documenting informed consent to ensure that adequate informed consent is obtained from participants.

The following procedures describe the requirements for obtaining consent from participants in research conducted under the auspices of the UNC-Chapel Hill.

2  Procedure

2.1  Basic Requirements

The requirement to obtain the legally effective informed consent of individuals before involving them in research is one of the central protections provided for by the Federal regulations and the UNC-Chapel Hill IRB. Investigators are required to obtain legally effective informed consent from a subject or the subject’s Legally Authorized Representative unless the requirement has been waived by the IRB. When informed consent is required, it must be sought prospectively, and properly documented.

The informed consent process involves three key features: (1) disclosing to the prospective human subject information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether or not to participate in the Research.

Informed consent is more than just a signature on a form. It is a process of information exchange to include reading, discussion, receiving answers to any questions, and signing the consent document. The informed consent process is the critical communication link between the prospective Human Subject and an Investigator, beginning with the initial approach of an Investigator and continuing through the completion of the Research study. Investigators must have received the appropriate training and be knowledgeable about the study Protocol in order
that they may answer questions to help provide understanding to the study participant or potential study participant. The exchange of information between the Investigator and study participant can occur via one or more of the following modes of communication, among others; face to face dialogue; mail; telephone; or fax; however, obtaining informed consent must allow for a dialogue so that the potential subject has the opportunity to ask questions and receive responses. Investigators must obtain consent prior to entering a subject into a study, gathering data about a subject, and/or conducting any procedures required by the research plan, unless consent is waived by the IRB.

If someone other than the investigator conducts the interview and obtains consent, the investigator needs to formally delegate this responsibility, and the person so delegated must have received appropriate training to perform this activity. The person so delegated must be knowledgeable about the research to be conducted and the consenting process, and must have the expertise be able to answer questions about the study including those regarding risks, procedures, and alternatives.

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

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

2.2 Informed Consent Process

Informed consent must be obtained under the following circumstances:

1. Informed consent may only be obtained from subjects who have the legal and mental capacity to give consent. For subjects without that capacity, permission must be obtained from a legal guardian or a legally authorized representative. See Section 2.3 below.

2. The informed consent process provides the prospective subject (or legally authorized representative) with sufficient opportunity to read the consent document, when applicable.

3. The informed consent process shall be sought under circumstances that provide the subject (or legally authorized representative) with sufficient opportunity to consider whether or not to participate.

4. The informed consent process shall be sought under circumstances that minimize the possibility of coercion or undue influence.

5. The informed consent information must be presented in language that is understandable to the subject (or legally authorized representative). To the extent possible, the language should be understandable by a person who is educated to 8th grade level and layman’s terms shall be used in the description of the research.

6. For subjects whose native language is not English, informed consent must be obtained in a language that is understandable to the subject (or the subject’s legally authorized
2.3 Who can act as a legally authorized representative (LAR) for a decisionally impaired research subject in North Carolina?

As is the case for most states, North Carolina does not have State legal statutes that specifically address research enrollment. In accordance with federal regulations and guidance from the OHRP, UNC-Chapel Hill has established that the informed consent laws applicable to clinical care in North Carolina (North Carolina General Statute 90-21.13) will be followed to determine who would be considered an acceptable LAR for purposes of providing surrogate consent for decisionally impaired subjects in studies conducted in North Carolina. Although the statute is specific to medical care, it may reasonably be applied to research participation as well.

In the case of an adult subject who lacks the capacity to consent, the LAR of the subject will be determined by taking the following individuals in this order of priority:

1. **Court-appointed legal guardian** (except to the extent any appointed health care agent has authority, unless the health care agent’s authority has been suspended by a court order) is a court appointed guardian granted "general" guardianship or "guardian of the person" may provide surrogate consent for all activities of the individual; therefore, this guardian may provide surrogate consent for research participation of the individual.

2. **A health care power of attorney (HCPOA)** is a health care agent pursuant to the execution of health care power of attorney document. A HCPOA document (to the extent of authority granted) grants the agent power to make health care decisions for the individual following a physician’s determination that the individual lacks adequate capacity to make her/his own health care decisions. Therefore, if such a physician determination has been made, the agent under an HCPOA may provide surrogate consent for research participation; to the extent this does not contradict the written HCPOA.

3. **A durable general power of attorney** grants the agent whatever authority is specified in the power of attorney document and is referred to as an attorney-in-fact. Where the power of attorney includes a specific provision stating that it shall survive any period of incapacity or mental incompetence of the principal it is considered a “durable” power of attorney, and the person holding power of attorney may provide surrogate consent for
Obtaining Informed Consent from Research Subjects

research participation unless the research participation includes an activity expressly excluded from the power of attorney. NOTE that a general power of attorney is only valid when registered with the register of deeds in either the county named in the power of attorney or the county in which the principal resides. Before relying on the decision of a person holding a general power of attorney, investigators should require proof that the power of attorney has been registered and should examine the document to ensure that it expressly survives any period of incapacity or mental incompetence of the principal. For assistance with these determinations, please contact the Office of University Counsel.

Where there is both a valid HCPOA and a valid general power of attorney, the person holding the HCPOA has priority over the person holding the general power of attorney in making decisions regarding participation in human subjects research.

(4) In the event that there is neither a court appointed guardian nor an agent under a durable general power of attorney or HCPOA, surrogate consent for research may be given, as long as there is no evidence to the contrary, by the other individuals listed below, in order of priority. When surrogate consent will be sought from one of these individuals, in the absence of a legal designation, their authority would be no broader (and may be more limited) than that of a duly appointed health care agent:

(4a) The subject’s spouse;

(4b) A majority of the subject’s reasonably available parents and adult children;

(4c) A majority of the subject’s reasonably available adult siblings; or

(4d) Another individual with an established relationship with the subject who is acting in good faith on behalf of the subject and can reliably convey the subject’s wishes.

To determine the authorized representative, refer to UNC Health Care System Policy ADMIN 0019, Authorized Representatives of Patients. If there is any doubt as to which individual is the legally appropriate authorized representative for the subject, the Office of University Counsel must be contacted.

NOTE: In the case of designations (1), (2) or (3) above, the investigator should obtain a copy of the court order, HCPOA, or durable power of attorney and should maintain the copy with the research records as documentation of the authority of the surrogate decision maker.

Beyond the categories described above, others may not give surrogate consent for research enrollment. Institutional custodians or caretakers are not legally authorized representatives in the absence of a specific court appointment granting them guardianship (see above).
2.4 Determining a potential adult subject’s ability to consent to research

In the absence of a specific legal or medical finding to the contrary, the individual subject must be presumed to have decision making power for himself/herself and must give consent, informed to the best ability of the research team. If there is any doubt as to the subject's capacity to consent, the investigator and the IRB should consider the need for independent assessment of capacity (e.g., psychiatric consult). If the subject does not have decisional capacity and the IRB has approved enrollment via surrogate consent, consent should be obtained from the highest available surrogate representative as described below.

There is an important distinction between the legal meaning of the term “incompetent” and our broader use of the term “decisionally impaired.” Decisionally impaired persons are those who, due to a psychiatric, organic, developmental or other disorder or situation that affects cognitive or emotional functions, are unable to exercise independent decision making. “Incompetence” is a finding of a court of law that results in the appointment of a legally authorized representative for the individual judged incompetent by the court (see “court appointed guardian” below). Persons who have been judged “incompetent” in a court of law are only a subset of the larger group of persons who may be decisionally impaired.

Decisional impairment in a human research subject may be determined by a court finding of incompetence, by a physician’s determination, or by a reasonable determination by the investigator or an independent consultant that the surrounding circumstances indicate that the individual is not able to exercise competent judgment about her/his personal risks and benefits in research participation. If a determination of decisional impairment is not confirmed by a court or physician, but only suspected, then consent should be obtained from both the subject and the appropriate representative.

For the purpose of this policy, a subject has the capacity to consent to his or her own participation in a research activity if s/he demonstrates an appreciation:

1. That the activity is research
2. Of the risks and benefits of a study
3. Of the study procedures and requirements
4. Of the alternatives that are available if not participating
5. That, by choosing not to participate, this decision will be accepted without penalty

In reaching a decision about participation, it is essential for the potential subject to demonstrate an ability to use this information in a rational manner. Thus, in considering risks, benefits, and available alternatives, subjects must show they understand the aspects of these factors that are unique to them as individuals.

See SOP 1201.7 for further discussion regarding adults who cannot consent for themselves.

The decision-making capacity of a potential research subject should be evaluated when there are reasons to believe that the subject may not be capable of making voluntary and informed decisions about research participation.
The investigator and research staff must have adequate procedures in place for assessing and ensuring subjects’ capacity, understanding, and informed consent or assent. The IRB will evaluate whether the proposed plan to assess capacity to consent is adequate including consideration of state and local law and organizational policy.

It is often possible for investigators and others to enable persons with some decisional impairments to make voluntary and informed decisions to consent, assent, or refuse participation in research. Potential measures include repetitive teaching, group sessions, audiovisual presentations, and oral or written recall tests. Other measures might include follow-up questions to assess subject understanding, videotaping or audio-taping of consent interviews, second opinions, use of independent consent observers, allowing a waiting period before enrollment, or involvement of a trusted family member or friend in the disclosure and decision making process.

Both investigators and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For subjects with fluctuating decision-making capacity or those with decreasing capacity to provide consent, periodic reevaluation of capacity and re-consent or consent for continuing participation by a legally authorized representative may be necessary.

In the event that research participants lose or become impaired in decision-making capacity after enrollment, and this is not anticipated in the research plan, the investigator is responsible for notifying the IRB. The investigator is responsible for developing a plan for the IRB’s consideration which follows the guidelines outlined above for persons with fluctuating or diminishing capacity.

Whenever the participants have the capacity to give consent (as determined by qualified professionals), informed consent should be obtained and document in accordance with Section 2.2 above. When participants lack the capacity to give consent, investigators may obtain consent from the legally authorized representative of a subject as described in SOP 1201.7.

When assent is possible for some or all subjects, the investigator should provide the IRB with an assent plan that describes when and how assent will be obtained, provisions that will be taken to promote understanding and voluntariness, and how assent will be documented. Under no circumstances may subjects be forced or coerced to participate.

If the investigator plans to use audio or videotapes, computer video presentations, or written materials, to promote understanding, these materials must be provided to the IRB for review. If the investigator intends to use audio or video recordings to document assent, provisions to ensure the security of the recordings should be described to the IRB. If the investigator will use an assent form to document assent, this must be submitted to the IRB for review.

2.5 Basic Elements of Informed Consent

To be valid, the consent process must provide the following basic elements of information to potential subjects:
1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

2. A description of any reasonably foreseeable risks or discomforts to the subject;

3. A description of any benefits to the subject or to others which may reasonably be expected from the research;

4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

5. A statement describing the extent, if any, to which confidentiality of records identifying the subject must be maintained;

6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects’ rights, and whom to contact in the event of a research-related injury to the subject;

8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled;

9. For FDA-regulated studies, a statement that notes the possibility that the Food and Drug Administration may inspect the records;

10. For “applicable” FDA-regulated clinical trials, the following statement must be included verbatim:

   “A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.”

In general, “applicable” clinical trials mean controlled clinical investigations, other than Phase 1 clinical investigations, of a drug or biologic; and prospective clinical studies of health outcomes comparing an intervention with a device against a control (other than (i) small clinical trials to determine the feasibility of a device, (ii) a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes, or (iii) mandated pediatric postmarket surveillance activities)

Additional elements of informed consent to be applied, as appropriate:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
2. Anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent;

3. Any additional costs to the subject that may result from participation in the research;

4. The consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject;

5. A statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject;

6. The approximate number of subjects involved in the study.

2.6 Documentation of Informed Consent

Except as provided in Section 2.10 of this document, informed consent must be documented by the use of a written consent form approved by the IRB.

1. Informed consent is documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject’s legally authorized representative at the time of consent. The person obtaining consent will also sign the consent form.

2. A copy of the signed and dated consent form must be given to the person signing the form. The investigator should retain the signed original in the research records.

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

A short form may be used when consenting non-English speakers or illiterate subjects. The short form should be used when you do not anticipate enrolling non-English speakers. If you anticipate enrolling non-English speakers, the consent form must be translated into the subject’s native language. The short form is not to be used when a study team has simply failed to make provisions for translated versions of the consent document in commonly spoken languages in the recruitment area/population. If the potential subject is blind, the consent form may be read to the person or the use of an audio version of the consent form (audiotape, digital audio format (e.g., MP3) should be considered.

Federal regulations (21 CFR 50.27(b)(2) and 45 CFR 46.117(b)(2) permits oral presentation of informed consent information in conjunction with a short form written consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally. A witness to the oral presentation is required and the subject must be given copies of both the short form document and the summary.
When this method of consent is used, there are additional regulatory requirements that must be followed. These include:

- The IRB must approve the full version of the consent form documents (or summary of information to be orally presented to the subject) including stored specimens and HIPAA authorization forms.

- The short forms available on the IRB website are considered IRB-approved documents. Several different languages are available. The short forms do not need to be submitted separately to the IRB for approval however only the study and contact information should be edited. The short form must be used in conjunction with the IRB-approved consent documents.

- A witness to the oral presentation must be present. The witness may be the interpreter, if one is used, or an independent third party. When consenting non-English speaking subjects, the witness must be bilingual in order to verify the exchange.

- **Required signatures:**
  - The short form must be signed by the subject (or subject’s representative) and the witness/interpreter.
  - The full version of the consent documents must be signed by the witness/interpreter and the person obtaining consent.

- At IRB Renewal: Report to the IRB, the number of times you used the short form to enroll subjects.

Investigators should carefully consider the ethical/legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented, the subject’s consent will not truly be informed and may not be legally effective. In addition, interpreters must be available for studies in which there is ongoing contact with the subject in order to facilitate study procedures, reporting of problems, etc.

### 2.7 Special Consent Circumstances

The IRB should include procedures to ensure that potential subjects are not excluded from potentially beneficial research due to barriers such as language and physical disabilities. At the same time, in order to ensure that subject welfare is protected throughout the participation, subjects should not be enrolled if they may not be able to communicate with the investigator on an ongoing basis.

#### 2.7.1 Enrollment of persons with limited English-language proficiency

1. Expected enrollment: In some studies, the investigator may be able to anticipate enrollment of persons who do not speak or read, or have limited proficiency in, oral or written English. When the target subject population includes such persons or the investigator and/or the IRB otherwise anticipates that consent will be conducted in a language other than English, the IRB requires a translated consent document, and other subject materials, to be prepared In
order to ensure that translated documents are accurate, the IRB may choose to require a
certified translation, to have an independent back-translation or to have a review of the
translated documents by an IRB member or other person who is fluent in that language. When
non-English speaking subjects enroll, they and a witness sign the translated consent document.
The subjects are given a copy of the signed translated consent document.

2. Unexpected enrollment: If a person who does not speak or read, or has limited
proficiency in, English presents for possible enrollment, an IRB-approved translated version of
the written consent may not be available for use. Investigators should carefully consider the
ethical and legal ramifications of enrolling subjects when a language barrier exists. If the
subject does not clearly understand the information presented during the consent process or in
subsequent discussions, his/her consent may not be informed, and therefore, not effective.
If an investigator decides to enroll a subject into a study for which there is not an extant IRB-
approved consent document in the prospective subject’s language, the investigator must
receive IRB approval to follow the procedures for a “short form” written consent in as
described in Section 2.6.

3. Use of interpreters in the consent process: Unless the person obtaining consent is fluent
in the prospective subject’s language, an interpreter will be necessary to facilitate the consent
discussion. Preferably someone who is independent of the subject (i.e., not a family member)
should assist in presenting information and obtaining consent. Whenever possible, interpreters
should be provided copies of the translated consent, or short form and the IRB-approved
consent script (typically the English-language version of the consent document) well before (24
to 48 hours if possible) the consent discussion with the subject. If the interpreter also serves as
the witness, she/he may sign the translated consent, or short form consent document and
script, as the witness and should note “Interpreter” under the signature line. The person
obtaining consent must document that the “short form” process was used in the subject's
research record, including the name of the interpreter.

2.7.2 Braille consent

For blind subjects who read Braille, the IRB may approve a consent document prepared in
Braille. In order to assure itself that a Braille consent document is accurate, the IRB may require
a transcription into print text or review of the document by an IRB member or other person
who reads Braille. If possible, the subject will sign the Braille consent; otherwise oral consent
will be obtained, witnessed and documented as described under “Oral Consent” (see Section
2.7.4).

2.7.3 Consenting in American Sign Language (ASL)

For deaf subjects who are fluent in ASL, the IRB may approve a consent process using ASL and
the IRB-approved written consent form. When this process is approved, the individual
authorized to consent prospective subjects must use the UNC-Chapel Hill-certified interpreter
fluent in ASL to conduct the consent process and the documentation of the consent process
must conform to the requirements set forth in Section 2.6.
2.7.4 Oral Consent

When subjects are unable to read a written consent form (such as blind or illiterate subjects), the IRB may approve an oral consent process, provided the subject (1) retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained orally and (2) is able to indicate approval or disapproval to study entry.

For research that is no more than minimal risk, documentation of consent may be waived according to the criteria in Section 2.9.

For greater than minimal risk research, the consent form must be read to the subjects and the subjects must be given an opportunity to ask questions. An audiotape approved by the IRB may also be used. If capable of doing so, the subject signs, or marks an X to signify consent. If that is not possible, the subject will provide oral consent. The person obtaining consent and a witness will sign the written study consent form with a statement that documents that an oral process was used and, if necessary, that the subject gave oral consent. The consent process will also be documented in the subject’s research record. Signed copies of the consent form are given to the subject and, whenever possible, these documents should be provided to the subject on audio or video-tape.

2.8 Subject Withdrawal or Termination

For a variety of reasons, a subject enrolled in a research study may decide to withdraw from the research, or an investigator may decide to terminate a subject’s participation in research regardless of whether the subject wishes to continue participating. Investigators must plan for the possibility that subjects will withdraw from research and include a discussion of what withdrawal will mean and how it will be handled in their research protocols/research plans and consent documents.

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

- For FDA-regulated clinical trials, when a subject withdraws from a study, the data collected on the subject to the point of withdrawal remain part of the study database and may not be removed. The consent document cannot give the subject the option of having data removed.

- For research not subject to FDA regulations, the investigator should inform subjects whether the investigator intends to either: (1) retain and analyze already collected data relating to the subject up to the time of subject withdrawal; or (2) honor a research subject’s request that the investigator destroy the subject’s data or that the investigator exclude the subject’s data from any analysis.

When a subject’s withdrawal request is limited to discontinuation of the primary interventional component of a research study, research activities involving other types of participation for which the subject previously gave consent may continue. Investigators should ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study.
Under this circumstance, the discussion with the subject would distinguish between study-related interventions and procedures and continued follow-up in person, by phone, or via records review, of data and address the maintenance of privacy and confidentiality of the subject's information.

If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up as described in the previous paragraph, the investigator must obtain the subject’s informed consent for this limited participation in the study (assuming such a situation was not described in the original consent document). IRB approval of consent documents for these purposes would be required.

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up, the investigator must not access or gather private information about the subject for purposes related to the study. However, an investigator may review study data related to the subject collected prior to the subject’s withdrawal from the study, and may consult public records, such as those establishing survival status.

### 2.9 Waiver of Informed Consent

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

(a) The research involves no more than minimal risk to the subjects;

(b) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(c) The research could not practicably be carried out without the waiver or alteration; and

(d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

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

(a) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

1. Public benefit or service programs;
2. Procedures for obtaining benefits or services under those programs;
3. Possible changes in or alternatives to those programs or procedures; or
4. Possible changes in methods or levels of payment for benefits or services under those programs; and,

(b) The research could not practicably be carried out without the waiver or alteration.
FDA regulations do not provide for waivers of informed consent except in certain emergency situations. Additionally, waivers of consent are not permissible for federally-funded research using Newborn Blood Spots.

2.10 Waiver of Documentation of Informed Consent

The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either that the:

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

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

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

2. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Procedures such as non-sensitive surveys, questionnaires and interviews generally do not require written consent when conducted by non-investigators (e.g., marketing surveys, telemarketing). Note: The FDA does permit a waiver of documentation of consent if this condition is satisfied. This is most commonly applied in the context of minimal risk screening activities that are necessary to determine eligibility for enrollment in the full trial.

Unless the IRB has granted a full waiver of the requirement to obtain informed consent, investigators who seek and receive approval for a waiver of documentation of consent still must perform an adequate consent process.

In cases in which the documentation requirement is waived, the IRB requires the investigator to provide in the application materials a written summary of the information to be communicated to the subject, and the IRB will consider whether to require the investigator to provide subjects with a written statement regarding the research. The IRB documents its findings justifying the waiver or alteration.

2.11 Waiver of Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergencies where the requirement to obtain prospective informed consent has been waived by the IRB is covered by 21 CFR §50.24 for FDA-regulated research and by the waiver articulated by DHHS at 61 FR 51531-33 for non-FDA-regulated research.

The FDA exception from informed consent requirements for emergency research under FDA regulations, 21 CFR 50.24, permits planned research in an emergency setting when human subjects who are in need of emergency medical intervention, cannot provide legally effective
informed consent themselves, and there is generally insufficient time and opportunity to locate and obtain consent from their legally authorized representatives (LARs).

The Secretary of Health and Human Services (DHHS) has implemented an Emergency Research Consent Waiver under 45 CFR 46.101(i) with provisions equivalent to those of the FDA with the exception of the requirements specified in Sections 2.11.2.1 and 2.11.2.2 below. The DHHS waiver is not applicable to research involving prisoners, pregnant women, fetuses, or in vitro fertilization.

2.11.1 Definitions

Planned Emergency Research. It is research that involves subjects who, are in a life-threatening situation for which available therapies or diagnostics are unproven or unsatisfactory, and because of the subjects' medical condition and the unavailability of legally authorized representatives of the subjects, it is generally not possible to obtain legally effective informed consent.

Family Member. For this section means any one of the following adult and legally competent persons: spouses; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

2.11.2 Procedures

The IRB may approve the planned emergency research without requiring informed consent of all research subjects prior to initiating the research intervention if the IRB finds and documents that the following conditions have been met:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:

(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 research.

(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 research are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The research could not practicably be carried out without the waiver.

(5) The proposed research plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sections 46.116 and 46.117 of 45 CFR 46 and Sections 50.20, 50.25 and 50.27 of 21 CFR 50. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject’s participation in the research consistent with paragraph (7)(v) of this section.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the research will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the research to apprise the community and investigators of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the research; 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 research. The investigator will summarize efforts made to contact
family members and make this information available to the IRB at the time of continuing review.

In addition, the IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the research, the details of the research and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the research and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into research with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the research is to be provided to the subject's legally authorized representative or family member, if feasible.

2.11.3 FDA-regulated Planned Emergency Research

1) A licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation must concur that the conditions described in Section 2.11.2 are satisfied.

2) Studies involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies that such studies may include subjects who are unable to consent. The submission of those studies in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35.

3) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided in the regulations or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly (no longer than within 30 days) 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.

4) The IRB determinations and documentation required in Section 2.11.2 and paragraph 3 above are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 56.115(b).
2.11.4 Planned Emergency Research Not Subject to FDA Regulations

1) The IRB responsible for the review, approval, and continuing review of the research has approved both the research and a waiver of informed consent and has (i) found and documented that the research is not subject to regulations codified by the FDA at 21 CFR Part 50, and (ii) found and documented and reported to the OHRP that the conditions required Section 2.11.2 have been met relative to the research.

2.12 Consent for use of stored samples and genetic testing

In general, all anticipated uses of collected samples of human tissues, body fluids, or biological products should be carefully delineated in the Procedures section of the consent form. Issues to be addressed might include the specific information to be obtained, whether the information may be of value to the subject, whether and how that information will be disclosed or made available to the human subject and whether genetic counseling will be available at the subject’s option.

If specimens are to be collected and stored for as yet unspecified purposes (genetic testing or otherwise), this should be addressed in the Procedures section of the consent form or in an addendum. The IRB will provide templates addressing these issues. Whether these templates must be included as an addendum to the consent form depends on the study. Generally, in cases where the primary purpose of the study is to store specimens or collection of specimens is not otherwise optional, then the addendum is unnecessary. Use of a separate addendum is generally preferred when storage of specimens is adjunct to the main purpose of the study and therefore optional.

The consent form and process for maintaining human specimens in a repository for future research uses must inform the subjects explicitly about the unspecified possible future use of the specimens and related personal information. The consent process should consider the following:

- The sample will be stored and possibly used in future research studies.
- A description of any personal information about the specimen source that will be maintained (this may or may not include identifiers).
- If no personal identifiers will be used for labeling the stored samples, i.e., if it is impossible for the sample to be linked with the subject, the consent form should so state.
- If personal identifiers are to be used that will allow future matching of the subject to the collected sample, the consent form should describe how they will be used, how privacy and confidentiality will be protected, and whether and under what circumstances identifying information would be disclosed.
- Future research using the samples will be reviewed by the IRB prior to additional use of the samples.
• Whether and how researchers may contact individuals whose specimens are in the repository
• A statement about any potential commercialization and that there are no plans for subjects to share in financial proceeds that may accrue from products derived from the specimens.
• Whether, how, and under what circumstance results from research studies using the specimens would be communicated to the subjects and, where relevant, to their family members).
• If specimens are individually identifiable, how the specimens and associated data may be withdrawn from the repository. If the specimens are not individually identifiable, a statement that they may not be withdrawn for that reason. Specimens that have already been used and the data derived from their use cannot generally be withdrawn.

2.13 Consent for inclusion in research registry

A research registry is a database of potential research subjects who have indicated their willingness to participate in research studies. Subjects must consent to inclusion in the registry. However, researchers may use a staged consent process in which preliminary consent is granted by subjects when they are included in the registry and additional consent is obtained when those subjects participate in a study.

2.14 Disposition of consent documents

As noted above, participants or their Legally Authorized Representative (LAR) must sign and date the consent form prior to participating in the study, unless this documentation is waived by the IRB. A copy of the signed consent form (photocopy or duplicate signed original) shall be given to the person signing the form. An original signed consent form should be retained in the investigator’s files.

2.14.1 Research consent forms in health care records

An informed consent document for research participation is not a health care document and ordinarily would not be included in a health care record. Similarly, other forms of information about research interventions that are not health care would not ordinarily be included in an individual’s health care record.

However, some clinical research includes health care. Additionally, information about some research interventions, whether or not treatment-related, may be relevant to a health care provider’s diagnosis and treatment decisions about the individual. For example, it may be important for a health care provider not associated with the research study to know that a patient is receiving drugs or interventions as part of a research protocol. In these circumstances it may be appropriate for the consent form to be included in the health care record.

At the time of the review, the IRB, in consultation with the PI, should make a determination as to the appropriateness of including the consent form in the health care record. Conversely, there may be circumstances where it is inappropriate to include the consent form in a subject’s
health care record, and specific mechanisms should be in place to exclude research information from the health care record (e.g., when research participation is not relevant to ongoing health care but might disclose sensitive personal information such as sexual preferences). If the decision is made to include the consent form in the health care record, then the informed consent and HIPAA authorization for the study should state that this information will be placed in the health care record.

In determining whether research participation records will be placed in the health care record, IRBs and investigators should consider several points. Although protection of the subject’s health and safety by providing research participation information to a health care provider is an appropriate concern, there are also other human subjects welfare issues to be considered, particularly privacy and confidentiality. Some human subjects will not want information about their research participation to be shared with their healthcare provider for a variety of reasons including personal privacy or the concern that the information may be transmitted to a health insurer or employer. These are the very privacy and confidentiality concerns that underlie the HIPAA regulations giving patients the right to know what is in their health care record and to control disclosure of their PHI from the health care record.

2.15 Record retention of informed consent forms

As with all protocol related materials, a copy of the approved consent documents (not the signed consent forms themselves) should be retained by the IRB for a minimum of three (3) years following the end of the study. For more information on storage of records, see IRB records requirements.

2.16 Collection of Social Security Numbers for Research Purposes

2.16.1 Introduction

There are occasions within the research setting when an investigator either needs to or is required to collect the social security number (SSN) or individual taxpayer identification number (ITIN) of a subject. Most often, the SSN (or ITIN) is collected as required by law, to comply with Internal Revenue Service (IRS) reporting requirements. Less often, the SSN (or ITIN) may be collected as a unique identifier to help match research datasets.

The North Carolina Identity Theft Protection Act imposes restrictions on the collection and disclosure of SSNs and other personal identifying information (PII). They also require segregation of SSNs and other security measures to protect PII.

2.16.2 Conditions for use of SSN in research

SSNs (or ITINs) collected for research must be relevant to the purpose for which they are collected, and shall not be collected until and unless the need for the SSN (or ITIN) has been clearly documented and approved by the IRB. When collecting the SSN (or ITIN), the investigator is required to provide a statement of the purpose or purposes for which the SSN
(or ITIN) is being collected and used. The SSN (or ITIN) may not be used for any purpose other than the purpose stated.

A subject must not be required to submit his or her SSN (or ITIN) over the Internet unless the connection is secure or the SSN (or ITIN) is encrypted. In addition, a subject’s SSN (or ITIN) must not be printed on materials that are mailed to him or her unless state or federal law requires that the SSN (or ITIN) be on the document(s) mailed.

### 2.16.3 IRB responsibilities

**Review and Approval of Proposed Use:**

The IRB has been designated to serve in lieu of the Social Security Number Management and Advisory Committee to review and approve collection of SSNs (or ITINs) and/or PII when required within the context of a research project.

The IRB may approve such collection for the following purposes:

1. Tax identification and other purposes mandated by federal or State laws. Per University policy, investigators are required to collect and report SSN and related information (as described below) when total payment(s) to an individual research subject will exceed $400 per calendar year.

2. Use as a unique identifier for a national registry or database where there is potential for duplicate registration and no other means of unique identification exists.

3. Matching existing records or specimens to those contained in another data set (SSNs or ITINs should be destroyed prior to data analysis).

4. Payment of medical expenses by a sponsor on behalf of a research subject.

Collection of the SSN (or ITIN) **may NOT** be approved for:

1. Use as an identifier when other means of unique identification would suffice.

2. Labeling of stored biological specimens.

3. Convenience.

4. An identifier to facilitate future contact with subjects.

**IRB Documentation**

The IRB will document the justification for collection of the SSN (or ITIN) and whether disclosure of the SSN (or ITIN) is voluntary or required for participation in the research.

### 2.16.4 Investigator responsibilities

**Mechanisms for Processing Payments to Subjects**

Researchers should be aware that the method used to compensate subjects may have an impact on the need to collect an SSN (or ITIN).
• Amounts that will total less than $400 per calendar year, investigators are not required to collect an SSN (or ITIN) if payments are made using a cash advance approach (e.g., gift cards or “petty cash” accounts).

• SSNs (or ITINs) must be collected for checks of any amount issued through the Accounts Payable system, even if that amount does not reach the $400 threshold because the University system requires the SSN (or ITIN) in order to “cut checks.”

• Investigators are also reminded that the IRS requires an SSN (or ITIN) to be collected and reported for payments of any amount to research subjects who are University employees.

SSN Collection Forms

• Investigators use the appropriate University-approved form to collect and store SSNs (or ITINs).

• The form states the purpose of collection and the planned use(s) of the SSN (or ITIN).

• The form also clarifies whether disclosure of the SSN (or ITIN) is voluntary or required for participation in the research; and/or required for payment of a medical claim by a sponsor on the subject’s behalf.

• If the SSN (or ITIN) is required solely for tax identification, the subject must be informed that (s)he has the right to renounce any research payment and consequently would not be required to disclose the SSN (or ITIN) in order to participate in the research study.

• If the SSN (or ITIN) is required for payment of a medical claim by a sponsor on the subject’s behalf, the subject must be informed that (s)he may refuse to provide the SSN (or ITIN) and decline the payment.

• The SSNs (and ITINs) authorization form must be segregated from the consent form. There are separate templates when the SSN (or ITIN) is collected for tax identification purposes, when the SSN (or ITIN) is used as a unique identifier to match datasets or when the SSN (or ITIN) is used for payment of a medical claim by a sponsor on a subject’s behalf. These templates may not be revised without the approval of the Office of University Counsel.

• Submit for IRB Approval:
  o If investigators know they will be required to collect an SSN or ITIN (e.g., because payments to subjects will exceed the stated threshold amounts) they should address this in the IRB application.
  o The IRB will review the justification for collecting the SSN (or ITIN).
  o It may also happen that the IRB identifies a previously-unrecognized need for collecting the SSN (or ITIN) while reviewing the study, in which case the investigator will be instructed accordingly.
  o Submissions that occur after the initial review should be submitted as a Modification, as with any change to an approved protocol.

• Storage and Disposition of Forms after SSN (or ITIN) Collection:
  o Investigators are expected to collect and store the signed SSN forms using appropriate security measures to protect the information.
If total payments to a participant do not exceed $400 by the end of the calendar year, the SSN forms should be destroyed (e.g., shredded), unless payments will continue and might reach that amount in subsequent years.

At the end of each calendar year, SSN forms for study participants who have been paid a total of more than $400.00 during the calendar year, should submit the completed SSN forms along with a separate list that includes the dollar amount paid to each subject, to Disbursement Services.

The SSN forms should be hand-delivered to the attention of the Director, Disbursement Services (located at 104 Airport Road, Suite 3500). If hand-delivery is not possible, the forms should be sent via campus mail or faxed (least preferred).

No study-related information is required by Disbursement Services, which should alleviate concerns about identities being linked to potentially-sensitive research topics by others outside the research team.

Disbursement Services will file necessary tax forms with the IRS and the individual (i.e., 1099-Misc).

Note: Researchers may elect to submit completed W-9 forms to Disbursement Services in lieu of SSN forms, in which case, the SSN forms should be destroyed. Regardless of which form is submitted to Disbursement Services, study participants must sign the appropriate SSN form.

Confidentiality:

SSNs and other PII must be maintained utilizing proper security measures to protect the information. Proper security measures include, for example, locked file cabinets in locked offices, password-protected electronic files, and encryption. An investigator or any other member of the research team may not intentionally communicate or otherwise make available to the general public a person’s SSN or other PII.

Breach of Confidentiality:
In the event of a security breach, as defined by the University’s “Data Security Breach Protocol,” (http://policies.unc.edu/policies/breach-protocol/) the matter must be reported immediately to the Information Technology Resources Center at 919-962-HELP or Campus Police at 919-962-8100, as specified in the Protocol.

Statement of Contractor Compliance:
When the IRB approves collection and disclosure of an SSN to an outside entity (e.g., research sponsors or database administrators), the outside receiving party must complete a Statement of Contractor Compliance with the North Carolina Identity Theft Protection Act of 2005. This signed form should be kept with the investigator’s study records.
2.16.5 DEFINITIONS:

Social Security Number (SSN) – SSN refers to the unique nine-digit number assigned by the United States government to individuals. For the purposes of this SOP, this also applies to the use of 4 or more digits of the SSN when accompanied by place and date of birth. This SOP also applies to circumstances where an individual subject (e.g., a worker who is not a US resident) has an Individual Tax Identification Number (ITIN) in lieu of an SSN.

Personal Identifying Information (PII) consists of:

1. SSN, ITIN or Employer Taxpayer Identification Numbers (EIN)
2. Driver’s license (unless appearing in a law enforcement record), State identification card, or passport numbers.
3. Checking account numbers.
4. Savings account numbers.
5. Credit card numbers.
6. Debit card numbers.
7. Personal Identification (PIN) codes, which are numeric and/or alphabetical codes assigned to the cardholder of a financial transaction card (FTC) by the issuer to permit authorized electronic use of that FTC.
8. Digital signatures.
9. Any other numbers or information that can be used to access a person's financial resources.
10. Biometric data
11. Fingerprints
12. Passwords

Legally Authorized Representative  A legally authorized representative is an individual or body authorized under applicable law to provide permission on behalf of a prospective subject to the subject’s participation in the procedure(s) involved in the research. For the purposes of this policy, a legally authorized representative includes.

Legal guardian. A person appointed by a court of appropriate jurisdiction.

3 References:

UNC Material & Disbursement Services:  http://www.unc.edu/mds/ds/help_hint.htm
NCGS §14-309.15 Raffles
1  Purpose

When some or all of the participants in a research conducted under the auspices of the University of North Carolina at Chapel Hill (UNC-Chapel Hill) are likely to be vulnerable to coercion or undue influence or have diminished decision-making capacity, the research must include additional safeguards to protect the rights and welfare of these participants. The IRB must ensure that all of the regulatory requirements for the protection of vulnerable subjects are met and that appropriate additional protections for vulnerable subjects are in place.

The following procedures describe the requirements for involving vulnerable participants in research under the auspices of the UNC-Chapel Hill.

2  Procedure

2.1  Involvement of Vulnerable Populations

If the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process should include one or more individuals who are knowledgeable about or experienced in working with these participants. The IRB may include one or more individuals who are knowledgeable about or experienced in working with individuals from these populations or it may seek such expertise through the use of consultants. 45 CFR 46 has additional subparts designed to provide extra protections for vulnerable populations which also have additional requirements for IRBs.

Subpart B - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Subpart C - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Subpart D - Additional Protections for Children Involved as Subjects in Research

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

In its FWA, the UNC-Chapel Hill limits its commitment to apply Subparts B, C, and D to non-exempt human subjects research conducted or supported by DHHS or any other federal agency that requires compliance with the Subpart(s) (B, C, or D) applicable to the research.
The following policies and procedures, which are based on Subparts B, C, and D, apply to all research regardless of funding. The individual sections describe how the subparts apply specifically to DHHS-funded research.

2.2 Responsibilities

1. The investigator is responsible for identifying the potential for enrolling vulnerable subjects in the research proposal, including the possible inclusion of subjects who are at risk for impaired decisional capacity, and who are being asked to participate in a research study with greater than minimal risk.

2. The IRB shall include representation, either as members or through the use of consultants, of individual(s) who are knowledgeable about or experienced working with the vulnerable populations involved in the research proposal under review.

3. The IRB reviews the investigator’s justifications for including vulnerable populations in the research to assess appropriateness for inclusion in the research proposal.

4. The IRB must ensure that appropriate additional safeguards have been included in each study to protect the rights and welfare of vulnerable subjects at the time of initial review of the research proposal.

5. Information reviewed as part of the continuing review process should include the number of participants considered to be members of specific vulnerable populations.

2.3 Review Procedures

2.3.1 Initial Review of Research Proposal

1. The investigator identifies the potential to enroll vulnerable subjects in the proposed research at initial review and provides the justification for their inclusion in the study.

2. The investigator describes safeguards to protect the subject’s rights and welfare in the research proposal.

3. The IRB evaluates the proposed safeguards, including, if applicable, the proposed plan for obtaining consent from legally authorized representatives and the plans for assent of children and adults unable to provide consent.

4. The IRB evaluates the research to determine the need for additional protections and considers, if appropriate, the use of a data and safety monitoring board, consent monitor, or research subject advocate.

2.3.2 Continuing Review and Monitoring

At Continuing Review the investigator should identify the number and categories of vulnerable subjects enrolled and any problems that arose relevant to their rights and welfare.
2.4 Research Involving Pregnant Women, Human Fetuses and Neonates

The following applies to all research regardless of funding source. According to the UNC-Chapel Hill FWA, Subpart B of 45 CFR 46 applies only to DHHS-funded research, the funding-source specific requirements are noted in the appropriate sections.

2.4.1 Research Involving Pregnant Women or Fetuses

2.4.1.1 Research Not Conducted or Supported by DHHS

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

Pregnant women or fetuses may be involved in research not funded by DHHS involving more than minimal risk to pregnant women and/or fetuses if all of the following conditions are met:

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus;
3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent;
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father’s consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children (as defined in Section 2.6) who are pregnant, assent and permission are obtained in accord with the requirements of state law and the IRB;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. Individuals engaged in the research have no part in determining the viability of a neonate.
2.4.1.2 Research Conducted or Supported by DHHS

For DHHS-conducted or supported research 45 CFR Subpart B applies to all non-exempt human subject research involving pregnant women, fetuses, and neonates.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent.
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father’s consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children (as defined in Section 2.5) who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 2.6.2;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

2.4.2 Research involving Neonates of Uncertain Viability or Nonviable Neonates

Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:
1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below in this section) have been met as applicable.

### 2.4.2.1 Neonates of Uncertain Viability

Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research unless the following additional conditions have been met:

The IRB determines that:

1. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or

2. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

3. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with the provisions of permission and assent, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

### 2.4.2.2 Nonviable Neonates

After delivery, nonviable neonates may not be involved in research unless all of the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained;

2. The research will not terminate the heartbeat or respiration of the neonate;

3. There will be no added risk to the neonate resulting from the research;

4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

5. The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply.
However, if either parent is unable to consent because of unavailability or incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph.

2.4.3 Viable Neonates

A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements for Research Involving Children (i.e., a viable neonate is a child for purposes of applying federal regulations and the UNC-Chapel Hill policies).

2.4.4 Research Involving, After Delivery, the Placenta, the Dead Fetus or Fetal Material

Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, must be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.

If information associated with material described above in this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent sections of these policies and procedures are applicable.

2.4.5 Research Not Otherwise Approvable

2.4.5.1 Research Not Conducted or Supported by DHHS

If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and the research is not approvable under the above provisions, then the IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on either:

1. That the research in fact satisfies the conditions detailed above, as applicable; or
2. The following:
   a. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
   b. The research will be conducted in accord with sound ethical principles; and
   c. Informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of this manual.
2.4.5.2 Research Conducted or Supported by DHHS

DHHS conducted or supported research that falls in this category must be approved by the Secretary of Health and Human Services. If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and the research is not approvable under the above provisions, then the research will be sent to OHRP for DHHS review.

2.5 Research Involving Prisoners

The following applies to all research involving prisoners, regardless of funding source. The requirements in this section are consistent with Subpart C of 45 CFR 46, which applies to DHHS-funded or supported research. When following Department of Justice regulations, for research conducted within the Bureau of Prisons: implementation of Bureau programmatic or operational initiatives made through pilot projects is not considered to be research.

2.5.1 Applicability

This policy applies to all biomedical and behavioral research conducted under the auspices of the UNC-Chapel Hill involving prisoners as subjects. Even though the IRB may approve a research study involving prisoners as subjects according to this policy, investigators are still subject to the Administrative Regulations of the NC Department of Corrections and any other applicable State or local law. [45 CFR 46.301]

2.5.2 Minimal Risk

Minimal risk, in studies involving prisoners, 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.

2.5.3 Composition of the IRB

In addition to satisfying the general membership requirements detailed in other sections of these policies and procedures, when reviewing research involving prisoners, the IRB must also meet the following requirements:

- A majority of the IRB (exclusive of prisoner members) must have no association with the prison(s) involved, apart from their membership on the IRB
- At least one member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement
- The prisoner representative must be a voting member of the IRB. A comment may be added to the roster indicating that the prisoner representative will only count
towards quorum when he or she is in attendance and reviewing studies covered by subpart C

2.5.4  **Review of Research Involving Prisoners**

1.  **Initial Review**
   a. The prisoner representative must review research involving prisoners, focusing on the requirements in Subpart C.
   b. The prisoner representative must receive all review materials pertaining to the research (same as primary reviewer).

2.  **Modifications**
   a. Minor modifications to research may be reviewed using the expedited procedure described below, using either of the two procedures described based on the type of modification.
   b. Modifications involving more than a minor change reviewed by the convened IRB must use the same procedures for initial review including the responsibility of the prisoner representative to review the modification and participate in the meeting (as described above).

3.  **Continuing review**
Continuing review must use the same procedures for initial review including the responsibility of the prisoner representative to review the continuing review materials and participate in the meeting (as described above).

4.  **Research Involving Prisoners, Reviewed by Expedited Review**
   a. Research involving interaction with prisoners may be reviewed by the expedited procedure, if a determination is made that the research involves no greater than minimal risk for the prison population being studied and the research falls within the categories of research eligible for expedited review.
   b. The prisoner representative must concur with the determination that the research involves no greater than minimal risk.
   c. The prisoner representative must review the research as a reviewer, designated by the chair, or consultant. This may be as the sole reviewer or in addition to another reviewer, as appropriate.
   d. Review of modifications and continuing review must use the same procedures as initial review.
   e. Research that does not involve interaction with prisoners (e.g., existing data, records review, etc.) may be reviewed by the expedited procedure, if a determination is made that the research involves no greater than minimal risk for the prison population being studied. Review by a prisoner representative is not required. The prisoner representative may review the research as a reviewer (if designated by the IRB Chair as
an expedited reviewer) or consultant. Review of modifications and continuing review will follow these same procedures.

5. **Research Involving Prisoners, Reviewed by the Convened IRB**

   a. The prisoner representative must present his/her review either orally or in writing at the convened meeting of the IRB when the research involving prisoners is reviewed.

   b. Continuing review – must use the same procedures for initial review including the responsibility of the prisoner representative to review the continuing review materials and participate in the meeting (as described above).

   c. If no subjects have been enrolled, the research may receive continuing review using the expedited procedure under expedited category #8.

### 2.5.5 Incarceration of Enrolled Subjects

If a participant becomes a prisoner while enrolled in a research study that was not reviewed according to Subpart C, the investigator must promptly notify the IRB and the IRB shall:

1. Confirm that the participant meets the definition of a prisoner.

2. Consult with the investigator to determine if it is in the best interests of the participant to continue participation in the study, in part or in full, and if so, if there are specific study activities which are in the best interests of the subject and should continue until the IRB is able to review the research study under Subpart C.

3. If the participant should continue, one of two options are available:

   a. Keep the participant enrolled in the study and review the research under Subpart C. If some of the requirements of Subpart C cannot be met or are not applicable (e.g., procedures for the selection of subjects within the prison), but it is in the best interests of the participant to remain in the study, keep the participant enrolled and inform OHRP of the decision along with the justification.

   b. Terminate enrollment of the participant from the study and keep the participant on the study intervention under an alternate mechanism such as compassionate use, off label use, etc.

4. If a participant is incarcerated temporarily while enrolled in a study:

   a. If the temporary incarceration has no effect on the study (i.e., there is no need for study activities to take place during the temporary incarceration), keep the participant enrolled.

   b. If the temporary incarceration has an effect on the study, follow the above guidance.
2.5.6 Additional Duties of the IRB

In addition to all other responsibilities prescribed for IRB in other sections of this manual, the IRB will review research involving prisoners and approve such research only if it finds that:

- The research falls into one of the following permitted categories [45 CFR 46.306(a)(2)]:
  
  - Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
  
  - Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
  
  - Research on conditions particularly affecting prisoners as a class (for example, research on diseases or social and psychological problems much more prevalent in prisons) provided that the study may proceed only after the DHHS Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research;
  
  - Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols/research plans approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the DHHS Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research;
  
  - Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
  
  - The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
  
  - Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the investigator provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
  
  - The information is presented in language which is understandable to the subject population;
  
  - Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is
clearly informed in advance that participation in the research will have no effect on his or her parole; and

• Where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing subjects of this fact.

2.5.7 Certification to DHHS

Under 45 CFR 46.305(c), the institution responsible for conducting research involving prisoners that is conducted or supported by DHHS shall certify to the Secretary (through OHRP) that the IRB has made the seven findings required under 45 CFR 46.305(a) and receive OHRP authorization prior to initiating any research involving prisoners. Certifications, and requests for DHHS Secretarial consultation, do not need to be submitted to OHRP for research not conducted or supported by DHHS, regardless of whether the institution has chosen to extend the applicability of its FWA and Subparts B, C, and D to all research.

For all DHHS conducted or supported research, OHRE Director will send to OHRP a certification letter to this effect, which will also include the name and address of the institution and specifically identify the research study in question and any relevant DHHS grant application or protocol/research plan. DHHS conducted or supported research involving prisoners as subjects may not proceed until OHRP issues its authorization in writing to the UNC-Chapel Hill on behalf of the Secretary under 45 CFR 46.306(a)(2).

Under its authority at 45 CFR 46.115(b), OHRP requires that the institution responsible for the conduct of the proposed research also submit to OHRP a copy of the research proposal so that OHRP can determine whether the proposed research involves one of the categories of research permissible under 45 CFR 46.306(a)(2), and if so, which one.

The term “research proposal” includes:

• The IRB-approved protocol/research plan; any relevant DHHS grant application or proposal;
• Any IRB application forms required by the IRB;
• And any other information requested or required by the IRB to be considered during initial IRB review.

OHRP also encourages the organization to include the following information in its prisoner research certification letter to facilitate processing:

• The OHRE Federalwide Assurance (FWA) number;
• The IRB registration number for the designated IRB; and
• The date(s) of IRB meeting(s) in which the study was considered, including a brief chronology that encompasses:
  o The date of initial IRB review; and
2.5.8 Waiver for Epidemiology Research

The DHHS Secretarial waiver for certain epidemiological research conducted or supported by DHHS functions as a fifth category of permissible research [68 FR 36929]. The criteria for this category are that the research must have as its sole purpose (i) to describe the prevalence or incidence of a disease by identifying all cases, or (ii) to study potential risk factor associations for a disease, and where the IRB has approved the research and fulfilled its duties under 45 CFR 46.305(a)(2)-(7) and determined that (i) the research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and (ii) prisoners are not a particular focus of the research. The specific type of epidemiological research subject to the waiver involves no more than minimal risk and no more than inconvenience to the human subject participants. The waiver would allow the conduct of minimal risk research that does not now fall within the categories set out in 45 CFR 46.306(a)(2).

The organization still must review the research under subpart C and certify to OHRP that an appropriately constituted IRB has reviewed the proposal and made all other required findings under DHHS regulations at 45 CFR 46.305(a) and receive OHRP authorization prior to initiating any research involving prisoners. All of the other requirements of subpart C apply to research in this category.

2.6 Research Involving Children

The following applies to all research involving children, regardless of funding source. The requirements in this section are consistent with Subpart D of 45 CFR 46, which applies to DHHS-funded research and Subpart D of 21 CFR 50, which applies to FDA-regulated research involving children. The IRB determines whether the criteria for approval of research are met when research involves children.

2.6.1 Allowable Categories

In addition to the IRB’s normal duties, research involving children must be reviewed by the IRB to determine if it fits within and is permissible under one or more federally-defined categories (OHRP/FDA). Each procedure or intervention that the child will undergo for the research must be taken into consideration. The categories are as follows:

1. [45 CFR 46.404/21 CFR 50.51] Research/Clinical Investigations not involving greater than minimal risk. Research determined to not involve greater than minimal risk to child subjects may be approved by the IRB only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in Section 2.6.2.

2. [45 CFR 46.405/21 CFR 50.52] Research/Clinical Investigations involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a
monitoring procedure that is likely to contribute to the subject’s well-being, may be approved by the IRB only if the IRB finds and documents that:

- The risk is justified by the anticipated benefit to the subjects;
- The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative options; and
- Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 2.6.2.

3. [45 CFR 46.406/21 CFR 50.53] Research/Clinical Investigations involving greater than minimal risk and no prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject’s disorder or condition. Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, may be approved by the IRB only if the IRB finds and documents that:

- The risk represents a minor increase over minimal risk;
- 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;
- The intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition which is of vital importance for the understanding or amelioration of the subjects’ disorder or condition; and
- Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 2.6.2.

4. [45 CFR 46.407/21 CFR 50.54] Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children.

When the IRB does not believe that the research meets the requirements of any of the above categories, and the IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the IRB shall refer the research for further review as follows:

- HHS conducted or supported research in this category will be referred for review by the Secretary of Health and Human Services. However, before doing so the IRB must determine and document that the proposed research also meets all of the requirements of the Common Rule.
- FDA-regulated research in this category will be referred for review by the Commissioner of Food and Drugs.
• The federal agency, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determined either:
  o That the research fell into categories [45 CFR 46.404/21 CFR 50.51], [45 CFR 46.405/21 CFR 50.52], [45 CFR 46.406/21 CFR 50.53]; or
  o The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children and the research will be conducted in accordance with sound ethical principles.
  o Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 2.6.2.

2.6.2 Parental Permission and Assent

2.6.2.1 Parental Permission

The IRB must determine that adequate provisions have been made for soliciting the permission of each child’s parent or guardian.

Parents or guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary, as described in SOP 1101.2.5.

The IRB may find that the permission of one parent is sufficient for research to be conducted under Categories 1 [45 CFR 46.404/21 CFR 50.51] & 2 [45 CFR 46.405/21 CFR 50.52] above. The IRB’s determination of whether permission must be obtained from one or both parents will be documented in the reviewer’s notes when a study receives expedited review, and in meeting minutes when reviewed by the convened committee.

Permission from both parents is required for research to be conducted under Categories 3 [45 CFR 46.406/21 CFR 50.53] & 4 [45 CFR 46.407/21 CFR 50.54] above unless

1. One parent is deceased, unknown, incompetent, or not reasonably available; or
2. When only one parent has legal responsibility for the care and custody of the child.

For research not covered by the FDA regulation, the IRB may waive the requirement for obtaining permission from a parent or legal guardian if:

• The research meets the provisions for waiver in SOP 1101.2.9 or
• If the IRB determines that the research is designed to study conditions in children or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children) provided that an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal, State, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described
in the protocol/research plan, the risk and anticipated benefit to the research subjects, and the child’s age, maturity, status, and condition.

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

Permission from parents or legal guardians must be documented in accordance with and to the extent required by SOP 1101.2.7.

2.6.2.2 Assent from Children

The IRB is responsible for determining that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. This judgment may be made for all children to be involved in the study, or for each child, as the IRB deems appropriate.

When the IRB determines that assent is not a requirement of some children, the IRB determines and documents which children are not required to assent. When the IRB determines that assent is not a requirement for some or all children, the IRB determines and documents one or more of the following:

- The children are not capable of providing assent based on the age, maturity, or psychological state. UNC does not require written assent from children six years of age or younger.
- The capability of the children is so limited that they cannot reasonably be consulted.
- 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 child and is available only in the context of the research.
- Assent can be waived using the criteria for waiver of the consent process.

It is important to note that the FDA regulations do permit the IRB to waive the assent requirement if it finds and documents that:

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

Because “assent” means a child’s affirmative agreement to participate in research, the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way.

The IRB should take into account the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects. For research activities involving adolescents whose capacity to understand resembles that of
adults, the assent procedure should likewise include information similar to what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity, but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (for example, what the experience will be, how long it will take, whether it might involve any pain or discomfort). The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve.

Parents and children will not always agree on whether the child should participate in research. Where the IRB has indicated that the assent of the child is required in order for him or her to be enrolled in the study, dissent from the child overrides permission from a parent. Similarly, a child typically cannot decide to be in research over the objections of a parent. There are individual exceptions to these guidelines but in general, children should not be forced to be research subjects, even when permission has been given by their parents.

2.6.2.2.1 Documentation of Assent

When the IRB determines that assent is required, it also is also responsible for determining whether and how assent must be documented. When the research targets the very young child or children unable or with limited capacity to read or write, an oral presentation accompanied perhaps by some pictures with documentation of assent by the person obtaining assent in a research note is likely more appropriate than providing the child a form to sign. In this case, the investigator should provide the IRB with a proposed script and any materials that they intend to use in explaining the research.

When the research targets children who are likely able to read and write, investigators should propose a process and form that is age appropriate and study specific, taking into account the typical child's experience and level of understanding, and composing a document that treats the child respectfully and conveys the essential information about the study. The assent form should:

1. Tell why the research is being conducted;
2. Describe what will happen and for how long or how often;
3. Say it's up to the child to participate and that it's okay to say no;
4. Explain if it will hurt and if so for how long and how often;
5. Say what the child's other choices are;
6. Describe any good things that might happen;
7. Say whether there is any compensation for participating; and
8. Ask for questions.
Whenever possible, the document should be limited to one page. Illustrations might be helpful, and larger type and other age appropriate improvements are encouraged when they have the potential to enhance comprehension. Studies involving older children or adolescents should include more information and may use more complex language.

### 2.6.3 Children Who are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406/21 CFR 50.53 or 45 CFR 46.407/21 CFR 50.54 (Categories 3 & 4 in Section 2.6.1), only if such research is:

1. Related to their status as wards; or
2. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

If the research meets the condition(s) above, an advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in loco parentis.

The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

### 2.7 Adults with Impaired Decision Making Capacity

The requirements in this section apply to all research involving adults who cannot provide consent or with impaired decision-making capacity regardless of funding source.

Research involving subjects without the ability to provide consent or with impaired decision-making capacity should only be conducted when the aims of the research cannot reasonably be achieved without their participation. Participation of such subjects in research cannot be justified solely on their availability or the convenience for the investigator.

When an investigator seeks to include such subjects in research, they must disclose this to the IRB and provide justification for why inclusion is necessary. If capacity to consent is questionable, or may fluctuate, investigators should include provisions for determining capacity to provide informed consent (See SOP 1101.2.4), and, if appropriate to reevaluate capacity during participation. When capacity to consent may diminish, the procedures should include, when possible and appropriate, designation of a legally-authorized authorized representative (LAR), inclusion of the future LAR in the initial consent discussion and process, and memorialization of the participant’s wishes regarding the research in writing. When the research includes subjects likely to regain capacity to consent, the investigator should include provisions to inform the subject regarding their participation and to seek consent for ongoing participation, if applicable.
When the IRB reviews research involving greater than minimal risk and the proposed subject population includes adults who cannot provide consent, may have impaired capacity to provide consent, or whose capacity can be expected to fluctuate over time, the IRB review process will include at least one member, or a consultant, who is experienced with or otherwise knowledgeable about the population.

In evaluating research, the IRB must be able to determine that the risks to subjects are reasonable not only in relation to any benefits, but also in relation to the importance of the knowledge that may reasonably be expected to result. In considering the risks of research involving subjects unable to provide informed consent or with diminished capacity to do so, the IRB should consider whether any components of the research involve risks that are greater for participants with diminished capacity. For example, the population might experience increased sensitivity or discomfort to certain stimuli or may not be able to verbalize or otherwise demonstrate when they are experiencing discomfort or pain.

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

1. Whether the aims of the research cannot reasonably be achieved without inclusion of the population
2. Whether the research is likely to improve the understanding of the condition, disease, or issue affecting the subject population
3. Whether any experimental procedure or interventions have undergone pre-clinical testing or human testing on other populations and whether the data from that testing supports its use in the proposed research
4. Whether the procedures or interventions that the subject will undergo in the research place them at increased risk and if appropriate mechanisms are in place to minimize risks, when possible
5. Whether the data and safety monitoring plan, including any stopping rules, is appropriate given the risks of the research and the vulnerability of the population
6. Whether the procedures for withdrawing individual subjects from the research are appropriate
7. Whether the recruitment procedures, consent process, and any plans for financial compensation support voluntariness and minimize the likelihood of undue influence or coercion
8. Whether the subjects will be exposed to financial or other risks that they might not consider acceptable if they had the capacity to provide consent, and whether appropriate mechanisms have been put into place to minimize these risks
9. Whether the procedures for determining capacity to provide consent, and for evaluating capacity on an ongoing basis, if applicable, are appropriate
10. Whether the procedures for informing subjects who regain capacity about their involvement in the research, and for obtaining consent for on-going participation, if applicable, are appropriate

11. Whether assent should be required when possible, and, if so, if the proposed procedures to obtain and document assent are appropriate

12. Whether a research subject advocate or consent monitor should be required, for some or all subjects

3 Definitions

Children. Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

According to North Carolina (NC) State Law, minors are persons under the age of eighteen. The general rule is that a person may consent for his or her own medical care at the age of eighteen. Therefore, the UNC-Chapel Hill IRB defines children as persons who are under eighteen years of age. Certain statutes and case law, however, provide minors with "majority" status in some circumstances, giving them the right to consent to their own medical care. For example: emancipated minors. NC law enumerates certain categories of individuals who, although under the age of 18, have the right to make medical decisions on their own behalf, such as minors who are married, widowed or divorced, minors who are parents, etc.); mature minors NC law recognizes that some minors may be sufficiently "mature" to give consent to medical treatment, even though they do not qualify as "emancipated"); or certain minors seeking care for drug addiction, sexually transmitted diseases, emotional disorders, or abortion or mental health treatment. Because NC law does not specifically address consent of children with majority status to research, the UNC-Chapel Hill will review issues of consent related to enrollment of these children in research on a case-by-case basis.

NOTE: For research conducted in jurisdictions other than NC, the research must comply with the laws regarding the legal age of consent in the relevant jurisdictions. The UNC-Chapel Hill’s Legal counsel will be consulted with regard to the laws in other jurisdictions.

Guardian. A guardian is an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.

In NC a “Guardian” of a child means the a court-appointed person with the duty and authority to act in the best interests of the minor, subject to residual parental rights and responsibilities, to make important decisions in matters having a permanent effect on the life and development of the minor and to be concerned with his or her general welfare. [NCGS 7B-3507 and NCGS 90-21.5(a,b).]

NOTE: For research conducted in jurisdictions other than NC, the research must comply with the laws regarding guardianship in all relevant jurisdictions. The UNC-Chapel Hill’s Legal counsel will be consulted with regard to the laws in other jurisdictions.
**Fetus.** A fetus means the product of conception from implantation until delivery.

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

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

**Neonate.** A neonate is a newborn.

**Viable.** As it pertains to the neonate, viable means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.

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

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

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


1. **Purpose**

FDA regulations apply to research that involves a FDA-regulated test article in a clinical investigation involving human subjects as defined by the FDA regulations. For FDA-regulated research, the IRB must apply the FDA regulations at 21 CFR 50 and 21 CFR 56. If required by organizational policy or a FWA, 45 CFR 46 must also be applied.

Clinical trials with investigational drugs must be conducted according to FDA’s IND regulations, 21 CFR Part 312, and other applicable FDA regulations. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA’s IDE regulations, 21 CFR Part 812, and other applicable FDA regulations.

The following procedures describe the review of FDA-regulated research conducted under the auspices of the University of North Carolina at Chapel Hill (UNC-Chapel Hill).

2. **Procedure**

2.1. **FDA Review Procedures**

A. At initial submission, the investigator must indicate whether the research involves a test article and is a clinical investigation involving human subjects on the application form. The investigator may use the IND Exemption Checklist to assist in making this determination.

B. During the pre-review process, the IRB Analyst will confirm whether FDA regulations are applicable using the IND Exemption Checklist. If FDA regulations apply and the research is not exempt, the IRB Analyst add the study to the next available full board agenda.

C. UNC-Chapel Hill follows ICH-GCP E6 to the extent it is consistent with FDA regulations.

2.2. **FDA Exemptions**

The following categories of clinical investigations are exempt from the requirements of FDA regulations for IRB review:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [21 CFR §56.104(c)]

2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient
at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR §56.104(d)]

2.3 Investigator Responsibilities

The investigator holds additional responsibilities when conducting a clinical trial evaluating FDA-regulated drugs, devices, and other articles. These responsibilities include, but are not limited to, the following:

1. The investigator is responsible for ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs (including biological products) or agreement for clinical investigations of medical devices, the investigational plan and other applicable regulations, and any requirements imposed by the IRB or FDA.

2. The investigator is responsible for personally conducting or supervising the investigation. When certain study-related tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

3. The investigator must maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (e.g., it can refer to an individual’s CV on file and/or training conducted by the investigator/sponsor), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.

4. The investigator is responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial. This responsibility includes:

   • Informing subjects that the test articles is being used for investigational purposes and ensuring that the requirements relating to obtaining informed consent are met
   • Providing reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention
   • Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, or when specialized care is needed)
   • Adhering to the protocol/research plan so that study subjects are not exposed to unreasonable risks
• As appropriate, informing the subject’s primary physician about the subject’s participation in the trial if the subject has a primary physician and the subject agrees to the primary physician being informed.

5. The investigator is responsible for reading and understanding the information in the investigator brochure or device risk information, including the potential risks and side effects of the drug or device.

6. The investigator is responsible for maintaining adequate and accurate records in accordance with FDA regulations and to making those records available for inspection by the FDA. These records include: correspondence with other investigators, the IRB, the sponsor, monitors, or the FDA; drug and device accountability records; case histories; consent forms; and documentation that consent was obtained prior to any participation in the study. Records must be obtained for a minimum of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such. Other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors may necessitate retention for a longer period of time.

7. The investigator is responsible for controlling drugs, biological products, and devices according to FDA regulations and the Controlled Substances Act, if applicable.

8. The investigator proposing the clinical investigation will be required to provide a plan that includes storage, security, and dispensing of the test article. This information may be documented in the IRB application or Master Protocol.
   
   a. If the test article is an investigational drug, according to the Joint Commission standards, Investigational Drug Services (IDS) must be used for storage, security, dispensing, administration, return, disposition, and records of accountability, unless there is an exception granted by IDS pharmacy, in which case, researchers must provide a written plan that describes the proper and safe handling of the investigational product to IDS.
   
   b. All devices received for a study must be stored in a locked environment under secure control with limited access. Proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use, and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.

9. The investigator shall furnish, upon request, all reports required by the sponsor of the research including adverse events, progress reports, safety reports, final reports, and financial disclosure reports.

10. The investigator will permit inspection of research records by the sponsor, sponsor representatives, HRPP and IRB representatives, the FDA, accrediting bodies, and any other agencies or individuals entitled to inspect such records under regulation, organizational policy, or contractual agreement.
2.4 Dietary Supplements

Research involving dietary supplements may or may not fall under FDA regulations. Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, a dietary supplement is not considered a drug and is not subject to the premarket approval requirements for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose). Whether a study falls under FDA oversight is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement’s effect on the structure or function of the body, FDA research regulations do not apply. However, if the study is intended to evaluate the dietary supplement’s ability to diagnose, cure, mitigate, treat, or prevent a disease, then FDA regulations do apply. Studies involving the ingestion of dietary supplements that are not subject to FDA oversight are still research, and therefore must be reviewed by the IRB.

Similarly, whether an IND is needed for a study evaluating a dietary supplement is determined by the intent of the study. If the study is intended only to evaluate the dietary supplement’s effect on the structure or function of the body, an IND is not required. However, if the study is intended to evaluate the dietary supplement’s ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required under part 312.

As with any research involving a test article, the investigator must supply the IRB with sufficient information to determine that the criteria for approval are satisfied and to determine or verify whether or not the research requires an IND. Applications should provide detail consistent with that expected on a drug protocol/research plan and consistent with the level of risk associated or anticipated with the research. At a minimum, the research plan should provide the following information regarding the supplement: Name, Manufacturer, Formulation, Dosage, Method/Route of Administration, Mechanism of Action, Known Drug Interactions, Risk Profile, IND number (or justification for why an IND is unnecessary), documentation of approval for use in humans, documentation or certification of Quality or Purity. As with drugs and devices there should be an accountability plan for the product describing where the product will be stored and how it will be dispensed, usage tracked, and disposal or return. If the study entails greater than minimal risk, a plan for Data and Safety Monitoring must be included.

2.5 Clinical Investigations of Drugs and Devices

2.5.1 IND/IDE Requirements

For studies evaluating the safety or effectiveness of medical devices or experiments using drugs, biologics, dietary supplements, and other compounds that may be considered a drug under FDA regulations, the investigator must indicate on the IRB application whether or not an IDE or IND is in place, and, if not, the basis for why an IDE or IND is not needed. Documentation must be provided by the sponsor or the sponsor-investigator. Documentation of the IND/IDE could be a:

1. Industry-sponsored study with IND/IDE number indicated on the protocol/research plan.
2. Letter/communication from FDA.
3. Letter/communication from industry sponsor.
4. Other document and/or communication verifying the IND/IDE.

For investigational devices, the study may be exempt from IDE requirements or, in the case of Non-significant Risk (NSR) device studies, follow abbreviated IDE requirements which do not require formal approval by the FDA. If a sponsor has identified a device study as exempt or NSR, then the investigator should include documentation with the submission providing the basis for exempt or NSR categorization. If the FDA has determined that the study is exempt or NSR, documentation of that determination must be provided.

The IRB will review the application and, based upon the documentation provided, determine: (1) that there is an approved IND/IDE in place, (2) that the FDA has determined that an IND is not required or that a device study is exempt or NSR, or, (3) if neither of the above, whether or not an IND is necessary, or that a device study is exempt or NSR, using the criteria below. The IRB cannot grant approval and research cannot begin, including recruiting, obtaining consent, and screening participants, until the IND/IDE status is determined, and, if necessary, an approved IND or IDE is in place. Please Note: An IND goes into effect 30 days after the FDA receives the IND, unless the sponsor receives earlier notice from the FDA.

2.5.1.1 IND Exemptions

For drugs, an IND is not necessary if the research falls in one of the following seven (7) categories:

1. The drug being used in the research is lawfully marketed in the United States and all of the following requirements are met:
   a. The research is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug
   b. In the case of a prescription drug, the research is not intended to support a significant change in the advertising for the product;
   c. The research does not involve a route of administration, dose, subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
   d. The research is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
   e. The research is conducted in compliance with the requirements of 21 CFR 312.7 (i.e., the research is not intended to promote or commercialize the drug product); and
   f. The research does not intend to invoke FDA regulations for planned emergency research [21 CFR 50.24].
2. The research only involves one or more of the following: (a) Blood grouping serum, (b) Reagent red blood cells or (c) Anti-human globulin;

3. For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and b) it is shipped in compliance with 312.160

4. A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

5. Bioavailability or Bioequivalence (BA/BE) studies if all of the following conditions are met:
   a. The drug product does not contain a new chemical entity [21 CFR 314.108], is not radioactively labeled, and is not cytotoxic;
   b. The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product;
   c. The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; and
   d. The sponsor meets the requirements for retention of test article samples [21 CFR 320.31(d)(1)] and safety reporting [21 CFR 320.31(d)(3)].

6. Research using a radioactive drug or biological product if all of the following conditions are met:
   a. It involves basic research not intended for immediate therapeutic, diagnostic, or similar purposes, or otherwise to determine the safety and efficacy of the product;
   b. The use in humans is approved by a Radioactive Drug Research Committee (RDRC) that is composed and approved by FDA;
   c. The dose to be administered is known not to cause any clinically detectable pharmacological effect in humans, and
   d. The total amount of radiation to be administered as part of the study is the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and is within specified limits.

7. FDA practices enforcement discretion for research using cold isotopes of unapproved drugs if all of the following conditions are met:
   a. The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry;
   b. The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject;
c. The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies;
d. The quality of the cold isotope meets relevant quality standards; and
e. The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively].

2.5.1.2 IDE Exemptions

For clinical investigations of devices, an IDE is not necessary if:

1. The research involves a device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time;

2. The research involves a device other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence (a “501k” device);

3. The research involves a diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
   a. Is noninvasive,
   b. Does not require an invasive sampling procedure that presents significant risk,
   c. Does not by design or intention introduce energy into a subject, and
   d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;

4. The research involves a device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;

5. The research involves a device intended solely for veterinary use;

6. The research involves a device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 812.5(c);

7. The research involves a custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

2.5.1.3 Significant and Non-Significant Risk Device Studies

A device study is a Non-Significant Risk (NSR) Device study if it is not IDE exempt and does not meet the definition of a Significant Risk (SR) Device study.
Under 21 CFR 812.3(m), an SR device means an investigational device that:

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

If the FDA has already determined a study to be SR or NSR, documentation evidencing such should be provided to the IRB. The FDA’s determination is final and the IRB does not have to make the device risk determination.

Unless the FDA has already made a device risk determination for the study, the IRB will review studies that the sponsor or investigator have put forth as NSR at a convened meeting to determine if the device represents SR or NSR.

The sponsor or sponsor-investigator is responsible for providing the IRB with an explanation describing the basis for their initial determination of NSR and any other information that may help the IRB in evaluating the risk of the study (e.g., reports of prior investigations of the device).

The IRB will review the information provided by the sponsor and investigator including, but not limited to: the sponsor or investigator’s NSR assessment, the description of the device, reports of prior investigations of the device (if applicable), the proposed investigational plan, and subject selection criteria.

The NSR/SR determination made by the IRB will be based on the proposed use of the device in the investigation, not on the device alone. The IRB will consider the nature of any harms that may result from use of the device, including potential harms from additional procedures subjects would need to undergo as part of the investigation (e.g., procedures for inserting, implanting, or deploying the device). The IRB may consult with the FDA or require the sponsor or investigator to obtain a determination from the FDA. The IRB will document the SR or NSR determination and the basis for it in the meeting minutes and provide the investigator, and sponsor when applicable, with the determination in writing.

Non-significant risk device studies do not require submission of an IDE application to the FDA but must be conducted in accordance with the abbreviated requirements of IDE regulations (21 CFR 812.2(b)). Under the abbreviated requirements, the following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under 812.20(a) that approval of an application is required:

1. An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor (or sponsor-investigator):
(i) Labels the device in accordance with 812.5;

(ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with an explanation of why the device is not a significant risk device, and maintains such approval;

(iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator’s care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under 56.109(c).

(iv) Complies with the requirements of 812.46 with respect to monitoring investigations;

(v) Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);

(vi) Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and

(vii) Complies with the prohibitions in 812.7 against promotion and other practices.

When the FDA or IRB determines that a study is SR, the IRB may approve the study, but the study cannot begin until an IDE is obtained.

### 2.6 Humanitarian Use Devices

A Humanitarian Use Device (HUD) is an approved (marketed) medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year [21 CFR 814.3(n)]. Federal law requires that IRBs approve the use of an HUD at a facility. Once approved, the clinical use of the HUD may be considered as any other approved device, with the caution that effectiveness has not been shown in clinical trials.

#### 2.6.1 Definitions

Humanitarian Device Exemption. A Humanitarian Device Exemption (HDE) is a “premarket approval application” submitted to FDA pursuant to Subpart A, 21 CFR Part 814 “seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the [FD&C Act] as authorized by section 520(m)(2) of the [FD&C Act].” HDE approval is based upon, among other criteria, a determination by FDA that the HUD will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

HDE Holder. An HDE Holder is a person who or entity that obtains to approval of an HDE from the FDA.
2.6.2 IRB Review Requirements

A Humanitarian Use Device (HUD) may only be used in a facility after an IRB has approved its use, except in certain emergencies. The HDE holder is responsible for ensuring that a HUD is provided only to facilities having an IRB constituted and acting in accordance with the FDA’s regulations governing IRBs (21 CFR Part 56), including continuing review of use of the device. When a HUD is used in a clinical investigation (i.e., research involving one or more subjects to determine the safety or effectiveness of the HUD), the full requirements for IRB review and informed consent apply (21 CFR 50 and 56) as well as other applicable regulations. It is essential to differentiate whether the HUD is being studied for the indication(s) in its approved labeling or for different indication(s). When the HUD is being studied for the indication(s) in its approved labeling, the IDE regulations at 21 CFR 812 do not apply. However, when the HUD is being studied for a different indication(s), 21 CFR 812 does apply, including the requirement for a FDA-approved IDE before starting the clinical investigation of a Significant Risk device.

2.6.3 Procedures

The relevant requirements and procedures for investigators and for IRB review described elsewhere in this manual apply to clinical investigations of HUDs. The material within this section applies to diagnostic or treatment uses of HUDs.

The health care provider seeking approval for diagnostic or treatment use of a HUD at the UNC-Chapel Hill is responsible for obtaining IRB approval prior to use of the HUD at the facility and for complying with the applicable regulations, including those for medical device reporting, institutional policies, and the requirements of the IRB.

Health care providers seeking initial IRB approval for diagnostic or treatment use of a HUD for the indication(s) in the HUDs approved labeling should submit the following materials to the IRB:

1. Humanitarian Use Device (HUD) Application Addendum
2. A copy of the HDE approval letter from the FDA
3. A description of the device, such as a device brochure
4. The patient information packet for the HUD
5. The proposed clinical consent process
6. Other relevant materials (e.g., training certificates) as identified in the Application Form

The IRB will review the proposal at a convened meeting ensuring that appropriate expertise is available either within the membership in attendance or via the use of consultants. The IRB will review the risks to patients that are described in the product labeling and other materials, the proposed procedures to ensure that risks are minimized, and will evaluate whether the risks are reasonable in relation to the potential benefits to patients at the facility. The IRB will evaluate
the patient information packet and proposed consent process and will determine if the materials are adequate and appropriate for the patient population.

The IRB may specify limitations on the use of the device, require additional screening and follow up procedures, require interim reports to the IRB, require continuing review more often than annually, or set other conditions or requirements as appropriate to minimize risks to patients and ensure the safe use of the device in the facility.

Once use of the HUD is approved, the health care provider is responsible for submitting any proposed changes to the IRB-approved plan or patient materials and obtaining approval for those changes prior to implementation, unless the change is necessary to avoid or mediate an apparent immediate risk to a patient. Proposed changes may be submitted by submitting a modification to the approved application and should be accompanied by any revised materials or supporting documentation. The IRB may review these changes using expedited review procedures or refer the changes for review by the convened IRB.

The health care provider is responsible for submitting reports to the FDA, the IRB, and the manufacturer/HDE Holder whenever a HUD may have caused or contributed to a death, and must submit reports to the manufacturer (or to FDA and the IRB if the manufacturer is unknown) whenever a HUD may have caused or contributed to a serious injury (21 CFR 803.30 and 814.126(a)). Serious injury means an injury or illness that (1) is life-threatening, (2) results in permanent impairment of a bodily function or permanent damage to a body structure, or (3) necessitates medical or surgical intervention to preclude permanent impairment of a bodily function or permanent damage to a body structure (21 CFR 803.3). The specific requirements for this reporting are in the Medical Device Reporting (MDR) Regulation, at 21 CFR Part 803. The IRB will review these reports via either expedited or convened review, as appropriate, and will consider whether any changes are needed to the IRB-approved plan or patient materials.

The health care provider is responsible for submitting continuing review materials to the IRB sufficiently in advance of the expiration date to ensure IRB review and re-approval prior to expiration. Materials to be submitted include:

1. The Continuing Review Report – Humanitarian Use Devices (non-research uses)
2. Any safety reports or summaries provided by the HDE holder that had not previously been submitted
3. The current patient information packet, if applicable
4. The current consent, if applicable
5. Other materials as identified on the Continuing Review Report
6. Any other new relevant information or materials

The IRB may conduct continuing review using expedited review procedures or review by the convened IRB.
2.6.4 Compassionate Use of off-label HUD

The IRB may approve, on a case-by-case basis, applications for the off-label emergency or compassionate use of a Humanitarian Use Device (HUD) based on a physician/principal investigator (PI) request that meets the following IRB criteria.

- The treating physician/investigator (PI) has determined that there is no alternative device for the patient's condition and there is no emergency.
- The PI has provided the HDE holder and the Medical IRB with the following:
  - A description of the patient’s condition and the circumstances necessitating treatment with the device;
  - A discussion of why alternative treatments are unsatisfactory; and
  - Assurances and information about patient protection measures.
- In addition, the PI shall request that the HDE holder submit an HDE amendment for FDA approval prior to the use of the device. If the FDA grants approval, the PI shall report the use of the HUD to the IRB and the HDE holder for subsequent submission to the FDA database.

Compassionate use shall be reviewed by the full IRB in a convened meeting using all standard full review criteria. In addition, the PI shall provide the HDE holder and the IRB with information addressing the criteria listed above. The approval applies to the single case requested and does not apply to a class of patients.

2.6.5 Emergency Uses of HUDs

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

If a HUD is approved for use in a facility, but an appropriately trained and licensed health care provider wants to use the HUD outside its approved indication(s) in an emergency or determines that there is no alternative device for a patient’s condition, the physician should consult with the HDE holder and IRB in advance if possible, obtain informed consent if possible, and ensure that reasonable measures are taken to protect the well-being of the patient such as a schedule and plan for follow up examinations and procedures to monitor the patient, taking into consideration the patient’s specific needs and what is known about the risks and benefits of the device. The provider should submit a follow up report to the HDE holder and the IRB and must comply with medical device reporting requirements.

The IRB may require additional reports, patient protection measures, or other requirement, as appropriate given the specifics of the situation.
2.7 Expanded Access to Investigational Drugs, Biologics, and Devices

Expanded access pathways, also referred to as “compassionate use”, are designed to make investigational medical products available as early in the drug and device evaluation process as possible to patients without therapeutic options, because they have exhausted or are not a good candidate for approved therapies and cannot enter a clinical trial. Expanded access refers to access to investigational medical products outside of a clinical trial, where the intent is treatment, rather than research. Because the investigational products have not yet been approved by FDA as safe and effective, it is important to remember that the product may not be effective and there may be unexpected serious adverse effects and to take appropriate measures to ensure that this is understood by the patient or their representative and to monitor for safety.

2.7.1 Expanded Access to Investigational Drugs and Biologics

The FDA’s expanded access rule for investigational drugs, including biologics classified as drugs, is intended to improve access to investigational drugs, and approved drugs with limited availability under a risk evaluation and mitigation strategy (REMS), for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and may benefit from the investigational diagnostic or therapy.

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

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

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

The FDA has also established a rule, “Charging for Investigational Drugs Under an Investigational New Drug Application”, to:

- Provide general criteria for authorizing charging for an investigational drug [21 CFR 312.8(a)]
- Provide criteria for charging for an investigational drug in a clinical trial [21 CFR 312.8(b)]
- Set forth criteria for charging for an investigational drug under the expanded access for treatment use
- Clarify what costs can be recovered

At UNC health care system, Investigational Drug Services (IDS) will be utilized for storage, security, dispensing, administration, return, disposition, and accountability of expanded access
investigational drugs. The investigator (or the holder of the IND) is responsible for drug procurement under the IND and will supply IDS with the investigational drug as necessary.

Investigators, when seeking access to drugs under the expanded access provisions, should work closely with the sponsor or manufacturer, the FDA, and the UNC-Chapel Hill OHRE, to determine the appropriate access mechanism and ensure that proper regulatory procedures are followed.

Unless the conditions that permit an emergency use exemption (see Section 13.9) are satisfied, prospective IRB review and approval is required for all expanded access uses, including clinical patient use. This requires, among other things, that the IRB review the expanded access use at a convened meeting at which a majority of IRB members are present.

### 2.7.2 Expanded Access to Investigational and Unapproved Medical Devices

As with investigational drugs, unapproved medical devices may normally only be used in humans in an approved clinical trial under the supervision of a participating clinical investigator. However, there may be circumstances under which a health care provider may wish to use an unapproved device when a patient is facing life-threatening circumstances or suffering from a serious disease or condition for which no other alternative therapy or diagnostic exists or is a satisfactory option for the patient.

FDA has made the following mechanisms available for these circumstances:

- Emergency Use
- Planned Emergency Research (See Section 11.11.1)
- Compassionate Use (or Single Patient/Small Group Access)
- Treatment Use
- Continued Access

Investigators, when seeking access to investigational or unapproved devices under one of the above provisions, should work closely with the sponsor or manufacturer, the FDA, and the UNC-Chapel Hill OHRE to ensure that proper regulatory procedures are followed.

Unless the conditions that permit an emergency use exemption are satisfied (see Section 13.9), prospective IRB review and approval is required. This requires, among other things, that the IRB review the proposed use at a convened meeting at which a majority of IRB members are present.

#### 2.7.2.1 Emergency Use

If an appropriately trained and licensed health care provider in an emergency situation determines that IRB approval for the use of an investigational drug/device at the facility cannot be obtained in time to prevent serious harm or death to a patient, the drug or device may be used without prior IRB approval. If the research involves an investigational drug, the FDA has issued an IND. The health care provider must, within 5 days after the emergency use of the
drug or device, provide written notification of the use to the IRB including information about
the patient involved (e.g., age, diagnosis, health status), the date of the use, and the reason for
the use.

Informed consent is not required when all of the following are true:

- Before the use of the test article both the investigator and a physician who is not
  otherwise participating in the clinical investigation certified the specific conditions in
  writing.
- The above written certification is submitted to the IRB within five working days after the
  use of the test article.
- Informed consent is not required because all of the following are true:
  - Immediate use of the test article is, in the investigator's opinion, required to
    preserve the life of the subject.
  - Time is not sufficient to obtain the independent determination a physician who
    is not otherwise participating in the clinical investigation.
  - Before the use of the test article, the investigator will certify the specific
    conditions in writing.

Note: DHHS regulations do not permit research activities to be started, even in an emergency,
without prior IRB approval. When emergency medical care is initiated without prior IRB review
and approval, the patient may not be considered a research subject under 45 CFR Part 46.
However, nothing in the DHHS regulations at 45 CFR Part 46 is intended to limit the authority of
a physician to provide emergency medical care, to the extent the physician is permitted to do
so under applicable federal, state or local law.

2.7.2.1.1 Emergency Exemption from Prospective IRB Approval

Under FDA regulations [21 CFR 56.104(c)], FDA exempts the emergency use of a test article
from the requirement for prospective IRB approval, provided that such emergency use is
reported to the IRB within 5 working days. Any subsequent use of the test article in the facility
requires IRB review. However, FDA acknowledges that it would be inappropriate to deny
emergency treatment to a second individual if the only obstacle is that the IRB has not had
sufficient time to convene a meeting to review the issue.

FDA defines emergency use as the use of a test article in a life-threatening situation in which no
standard acceptable treatment is available, and in which there is not sufficient time to obtain
IRB approval [21 CFR 56.102(d)]. If all conditions described in 21 CFR 56.102(d) exist then the
emergency exemption from prospective IRB approval found at 21 CFR 56.104(c) may be used.
The emergency use of a test article, other than a medical device, is a clinical investigation, the
patient is a participant, and the FDA may require data from an emergency use to be reported in
a marketing application.

Life-threatening, for the purposes of 21 CFR 56.102(d), includes both life-threatening and
severely debilitating.
Unless the provisions for an emergency exception from the informed consent requirement are satisfied (see Section 13.9.2), informed consent must be obtained in accordance with 21 CFR 50 and documented in writing in accordance with 21 CFR 50.27.

The IRB must be notified within 5 working days when an emergency exemption is used via the submission of a “Report of Emergency Use of a Test Article” form. The IRB Chair or designated member will review the report to verify that circumstances of the emergency use conformed to FDA regulations. This must not be construed as an approval for the emergency use by the IRB, as an exemption from the requirement for prospective IRB approval has been invoked. When appropriate, in the event a manufacturer requires documentation from the IRB, the IRB will provide a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Reports of emergency uses will be brought to the convened IRB for their information. Investigators are reminded that they must comply with all other organizational policies and requirements applicable to the use of the investigational or unapproved article.

2.7.2.1.2 Emergency Exception from the Informed Consent Requirement

An exception under FDA regulations at 21 CFR 50.23(a-c) permits the emergency use of an investigational or unapproved test article without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

a. The subject is confronted by a life-threatening situation necessitating the use of the test article;

b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;

c. Time is not sufficient to obtain consent form the subject's legally authorized representative; and

d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the life of the subject.

If immediate use of the test article is, in the investigator’s opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent physician determination in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

The IRB must be notified within 5 working days when an emergency exception is used via the submission of a “Report of Emergency Use of a Test Article” form. Documentation of the independent physician evaluation must be provided. The IRB Chair or designated member will review the report to verify that circumstances of the emergency exception conformed to FDA regulations.
2.7.2.1.3 Waiver of Informed Consent for Planned Emergency Research

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

See SOP 1101.2.1 for additional detail on Planned Emergency Research.

2.8 Use of test articles in research: INDs or IDEs Investigational New Drug and Investigational Device Exemption studies

An Investigational New Drug (IND) Application or Investigational Device Exemption (IDE) are exemptions from the law that otherwise requires that a drug, biologic, or device must be approved before it can be transported across state lines. Generally, one of these exemptions is required whenever a research study uses a drug, biologic or significant risk device that has not received FDA marketing approval. An IND may also be required for a drug that does have FDA marketing approval if the research study proposes a use of the drug that was not included in the existing FDA approval. (See the FDA Information Sheets on "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices" for additional requirements.) IND and IDE research studies are subject to the same new and continuing review requirements as for human subjects research in general, but they also require FDA approval for the proposed research use.

Most IND and IDE studies at the University are research protocols developed and sponsored by the commercial entity that is developing a drug or device pursuant to FDA regulations and is itself responsible for obtaining the IND or IDE approvals and for fulfilling all other FDA requirements for such a study. There are some IND or IDE studies for which the study protocol has been developed independently by a university investigator and for which that investigator is responsible for obtaining the IND or IDE and for fulfilling all FDA required filings and other documentation. Investigators should contact the Office of Clinical Trials for guidance and support regarding IND and IDE studies.

Investigators will provide the IND or IDE number as a part of the IRB application; the IRB primary reviewer should verify that the IND or IDE number is valid by assuring consistency across documents (e.g., FDA letters, sponsor protocol).

The IRB is not required to monitor the investigator’s performance of required FDA paperwork. However, in reviewing the study, the IRB should be mindful that in this context, the IRB review should include a determination of whether an IND or IDE is required and may also require more intense IRB scrutiny of the protocol and related risks as well as more guidance to the investigator regarding the scientific design, subject safety parameters, informed consent process and other human subjects protection factors.

For non-emergency situations, prospective IRB approval is required. Single patient use allows a physician to obtain access to an investigational drug upon receiving approval from the IRB. This
approval is granted for the treatment of a single patient. The treatment use may occur only after IRB approval is obtained.

2.8.1 Compliance with IND regulations

When research involves the use of a drug other than the use of a marketed drug in the course of normal medical practice, the University will confirm that:

- The drug has an IND; or
- The protocol meets one of the FDA exemptions from the requirement to have an IND:

Exemption 1

- The drug product is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.
- If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product.
- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- The investigation will be conducted in compliance with 21 CFR 50 and 56.
- The investigation will be conducted in compliance with the requirements of 21 CFR 312.7.

Exemption 2

- A clinical investigation is for an in vitro diagnostic biological product that involves one or more of the following:
  - Blood grouping serum.
  - Reagent red blood cells.
  - Anti-human globulin.
- The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.
- The diagnostic test will be shipped in compliance with 21 CFR 312.160.

Exemption 3

- A drug intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.160.
Exemption 4

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

2.8.2 Compliance with IDE regulations

When research is conducted to determine the safety or effectiveness of a device, the University will confirm that:

• The device has an IDE issued by the FDA; or
• The device fulfilled the requirements for an abbreviated IDE:
  ▪ The device is not a banned device.
  ▪ The sponsor labels the device in accordance with 21 CFR 812.5.
  ▪ The sponsor will obtain IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval.
  ▪ The sponsor will ensure that each investigator participating in an investigation of the device obtains from each subject under the investigator’s care, consent under 21 CFR 50 and documents it, unless documentation is waived.
  ▪ The sponsor will comply with the requirements of 21 CFR 812.46 with respect to monitoring investigations;
  ▪ The sponsor will maintain the records required under 21 CFR 812.140(b) (4) and (5) and report as required under 21 CFR 812.150(b) (1) through (3) and (5) through (10);
  ▪ The sponsor will ensure that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and report as required under 812.150(a) (1), (2), (5), and (7); and
  ▪ The sponsor will comply with the prohibitions in 21 CFR 812.7 against promotion and other practices; or
• 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 the FDA had determined to be substantially equivalent to a device in commercial distribution immediately
before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

- A diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
  - Is noninvasive.
  - Does not require an invasive sampling procedure that presents significant risk.
  - Does not by design or intention introduce energy into a participant.
  - 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 participants at risk.
  - A custom device as defined in 21 CFR 812.3(b), unless the device was being used to determine safety or effectiveness for commercial distribution.

### 2.8.3 Humanitarian Use Device

FDA regulations define a “humanitarian use device” ("HUD") as a device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States per year. Because of the extremely limited market for such devices, they do not receive full FDA review and approval. For this reason FDA requires prospective IRB approval (except in exceptional emergency situations for any use of the HUD with human research subjects or with patients. The investigator or health care provider is required to submit an application for IRB review of the proposed HUD use. Included in the application must be evidence that the investigator/sponsor has obtained a Humanitarian Device Exemption (HDE) from the FDA in accordance with 21 CFR 814.100-126.

While the effectiveness of the device does not have to be demonstrated, the IRB will verify that the device does not pose an unreasonable risk of illness or injury to the recipient, and that the probable benefit to health 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. The IRB approval must verify that the use of the HUD, as proposed, is consistent with current labeling of the device and does not exceed the scope of the FDA approved indication. The device’s labeling must state that the device is a humanitarian use device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been proven or demonstrated. The initial review of a HUD is to be completed by a convened IRB. The IRB may approve use of the HUD without any further restrictions, or under a protocol, or on a case-by-case basis. The convened Board may make the
determination at initial review that continuing review may occur using the expedited procedure if the HUD is not being used in the course of a research study. Criteria the IRB may use to grant continuing review using the expedited procedure include: initial use of the HUD was approved without any further restrictions, and the continuing review period was not less than 1 year. Criteria for subsequent continuing review using the expedited procedure may include: there have been no subject complaints, and no additional risks have been identified.

FDA regulations do not require informed consent for patient care uses of a HUD; in these cases there will be no “research consent form” and consent should be obtained in accordance with UNC Healthcare policies and practices. When the HUD is being used in a research study, consent should be obtained in accordance with research policies and practices.

2.8.4 Investigational Drug Service (IDS)

An agent/drug (including supplements) will be considered investigational if both the following two criteria are met: 1) administration of the agent is part of a protocol that requires IRB approval, and 2) a subject is required to sign an Informed Consent Form before receiving the agent. Researchers using investigational drugs in studies must register all studies with and, if appropriate, use the services of, the IDS Pharmacy. (See http://pharmacy.intranet.unchartedcare.org/services/investdrugs)

The IDS pharmacists coordinate the preparation and dispensing of clinical trial medications, to the extent possible, within the framework of existing policies and procedures of the Department of Pharmacy. In addition, IDS pharmacists assist investigators in the design of clinical trials, which include the blinding and randomization of drug therapies. IDS pharmacists maintain inventory and dispensing records, ensure compliance with State laws and federal regulations for the handling of investigational drugs, and provide drug information to medical and nursing personnel.

2.8.4.1 Storage and control of investigational devices

Investigational devices will be stored, controlled and dispensed in accordance with UNC Health Care System policy, once enacted. Pursuant to this policy, the investigator will describe the plan for storage, control, and dispensing of the device. The department of the investigator will be responsible for reviewing the plan and evaluating whether it is adequate to ensure that only authorized investigators will use the device and they will use the device only in participants who have provided consent.

Definitions

**Biologic.** Biological products include a wide range of products such as vaccines, blood and blood components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other technologies. In general, the term "drugs" includes therapeutic biological products.
**Dietary Supplement.** A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains a dietary ingredient. The dietary ingredients in these products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. See section 201(ff) of the FD&C Act [21 U.S.C. 321(ff)].

**Investigational Drug.** Investigational or experimental drugs are new drugs that have not yet been approved by the FDA or approved drugs that are being studied in a clinical investigation.

**Investigational Device.** Investigational device means a device (including a transitional device) that is the object of an investigation. Investigation, as it pertains to devices, means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

**IND.** IND means an investigational new drug application in accordance with 21 CFR Part 312.

**IDE.** IDE means an investigational device exemption in accordance with 21 CFR 812.

**In Vitro Diagnostic Product (IVD).** In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. [21 CFR 809.3(a)]

**Emergency Use.** Emergency use is defined as the use of an investigational product with 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. [21CFR 56.102(d)]

**Significant Risk (SR) Device.** Significant risk device means an investigational device that:

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

**Non-Significant Risk (NSR) Device.** A non-significant risk device is an investigational device that does not meet the definition of a significant risk device.

**Humanitarian Use Device (HUD).** A Humanitarian Use Device is a device intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.
1 PURPOSE
1.1 Regulations require an organization to have written procedures for ensuring prompt reporting of changes in research activity; unanticipated problems involving risk to subjects or others; and any instances of serious or continuing non-compliance to the IRB, organizational officials, and applicable federal agencies. In order to comply with this requirement, the UNC-Chapel Hill has procedures to review issues that arise during the conduct of human subjects research conducted under the aegis of UNC-Chapel Hill. This policy describes the safety information that is promptly reportable to the Office of Human Research Ethics (OHRE).

2 RESPONSIBILITY
2.1 Researchers carry out these procedures.
2.2 The PI is responsible for reviewing and certifying new safety information prior to submission.

3 PROCEDURE
3.1 Reporting Requirements
Information previously unknown to the IRB that suggests new or increased risk to subjects or others (hereinafter referred to as New Safety Information) is promptly reportable to OHRE within 7 calendar days of the investigator becoming aware of the information. TABLE 1, New Safety Information, outlines the type of information that constitutes New Safety Information. Detailed examples of New Safety Information are provided in SUPPLEMENT 1.

3.1.1 Protocol deviations that did not harm subject(s) or others or place subject(s) or others at increased risk should be documented by the investigator in a deviation log. This log is subject to review by the IRB of other agency of the UNC-CH HRPP.

3.1.2 Researchers may consult with the OHRE Compliance Manager if they are uncertain about what information is reportable.
**TABLE 1, New Safety Information**

<table>
<thead>
<tr>
<th>Reporting Requirements for studies for which the UNC IRB has oversight responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal adverse events that are (1) unexpected, (2) related or possibly related to participation in the research, and (3) serious or suggest that there are new or increased risk(s) to subjects.</td>
</tr>
<tr>
<td>External adverse events that are (1) unexpected, (2) related or possibly related to participation in the research, (3) serious or suggest that there are new or increased risk(s) to subjects, and (4) warrant a change to the protocol or consent or subject notification (See 3.3 for additional information).</td>
</tr>
<tr>
<td>Interim analysis, data and safety monitoring report, findings from other studies, findings from animal or in-vitro testing, or other finding(s) that indicate (1) there are new or increased risks to subjects or others, or (2) subjects are less likely to receive any direct benefits from the research.</td>
</tr>
<tr>
<td>Unanticipated adverse device effect</td>
</tr>
<tr>
<td>Protocol deviation that harmed subject(s) or others or placed subject(s) or others at increased risk of harm. <strong>All other protocol deviations should be documented by the investigator in a deviation log. This log is subject to review by the IRB of other agency of the UNC-CH HRPP.</strong></td>
</tr>
<tr>
<td>Protocol deviation that is made to eliminate an immediate hazard to a subject without IRB approval</td>
</tr>
<tr>
<td>Intentional or unintentional failure to follow applicable federal human subject protection regulations, the requirements or determinations of the IRB, the IRB-approved study protocol, or University policies when that failure adversely affects the rights or welfare of participants, such as:</td>
</tr>
<tr>
<td>• Conducting human subjects research without an IRB-approved protocol or exemption</td>
</tr>
<tr>
<td>• Starting research prior to meeting the conditions required by the IRB and receiving an IRB notification of approval, or conducting research during a lapse in approval</td>
</tr>
<tr>
<td>• Failure to obtain informed consent</td>
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<tr>
<td>• Deviating from the informed consent or recruitment process approved by the IRB</td>
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<tr>
<td>• Failure to provide a participant with new information about study risks or procedures that may affect the participant’s willingness to continue/participate in the study (i.e., by not reconsenting participants or by using an old version of a consent document to consent a new participant)</td>
</tr>
<tr>
<td>• Initiating changes to the protocol without IRB approval, including using unapproved materials (e.g., fact or information sheets, recruitment materials, questionnaires, focus group guides, scripts, or other materials provided to participants)</td>
</tr>
<tr>
<td>• Failure to complete IRB- or institutionally-required human subjects protection training prior to engaging in human subjects research</td>
</tr>
<tr>
<td>• Enrollment of participants beyond what has been approved by the IRB in a study that is greater than minimal risk</td>
</tr>
<tr>
<td>Breach or potential breach of subject confidentiality or privacy.</td>
</tr>
<tr>
<td>Complaint by or on behalf of a research subject that (1) indicates that the rights, welfare, or safety of the subject have been adversely affected, or (2) cannot be resolved by the investigator. Subject complaints about payment should be resolved by the study team.</td>
</tr>
<tr>
<td>Allegation of noncompliance</td>
</tr>
<tr>
<td>Audit, inspection, or inquiry by a federal agency</td>
</tr>
<tr>
<td>Written report from a federal agency (e.g., FDA Form 483)</td>
</tr>
<tr>
<td>State board action that (1) will affect the ability to conduct or complete the research as approved by the IRB or (2) increases risks to subjects or others (e.g., suspension of professional license)</td>
</tr>
<tr>
<td>Incarceration of a subject enrolled in a research study that is not approved to involve prisoners</td>
</tr>
<tr>
<td>Institution-, investigator-, or sponsor-initiated hold or early closure as a result of safety concerns</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reporting requirements for studies ceding IRB review and oversight to an external IRB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO) or Serious Noncompliance or Continuing Noncompliance determinations by an external IRB to which UNC cedes IRB review and oversight when the event involved UNC subjects or researchers</td>
</tr>
<tr>
<td>Suspension or termination by an external IRB to which UNC cedes IRB review and oversight</td>
</tr>
</tbody>
</table>
3.2 Reporting will flow as indicated in Figure 1; however, there may be instances where an alternative order of reporting is appropriate.

Figure 1, Steps to Reporting New Safety Information
3.2.1 Immediate Corrections
The first step is for investigators to eliminate immediate hazard to subject(s) or others. Immediate corrections does not require IRB approval prior to initiation, but should be described in the initial report of New Safety Information.

3.2.2 Assessment of Risk
Actual harm does not have to occur in order for there to be increased risk of physical, psychological, social, legal, or economic harm. The investigator’s assessment of risk should be specific to the event, not the study overall, and it should be independent of benefit. An event that increases risk to subjects or others changes the risk/benefit ratio, but it may or may not change the IRB’s assessment that the risks are reasonable in relation to the anticipated benefit(s), if any, to the subjects.

3.2.2.1 Assessment of risk of an adverse event. The first step in assessing whether an adverse event suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized is to determine whether the adverse event is serious.

3.2.2.1.1 For the purposes of this SOP, the adverse event is serious when the outcome for the subject is:
- death;
- life-threatening (places the subject at immediate risk of death from the event as it occurred);
- inpatient hospitalization or prolongation of existing hospitalization;
- persistent or significant disability/incapacity;
- congenital anomaly/birth defect; or when the event does not fit the other outcomes but, based upon appropriate medical judgment, may jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the other outcomes (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, persistent blood abnormality or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse). (Modified from the definition of serious adverse drug experience in FDA regulations at 21 CFR 312.32(a), and OHRP guidance: “Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events,” January 15, 2007)
3.2.2.1.2 OHRP and FDA consider adverse events that are unexpected, related or possibly related to participation in research, and serious to be the most important subset of adverse events representing unanticipated problems because such events always suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized and routinely warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subject. (See examples 1 and 2 in SUPPLEMENT 1).

3.2.2.1.3 However, 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. Again, such events routinely warrant consideration of substantive changes in 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 (see examples 3 and 4 in SUPPLEMENT 1).

3.2.3 Initial Report to the IRB
Investigators must report New Safety Information to OHRE in IRBIS. Generally, the report should contain the following:

3.2.3.1 Detailed information about the event or issue, including relevant dates. The report should identify the affected subjects by their study codes and not by their names or other personal identifiers.

3.2.3.2 An assessment of whether any subjects or others were placed at risk or suffered any harm (e.g., physical, social, financial, legal or psychological) as a result of the event.

3.2.3.3 If the event involves noncompliance, describe the result of the root cause analysis. For more details about root cause analysis see 3.2.4.

3.2.3.4 Any corrective and preventative actions, planned or already taken.

3.2.3.5 Any other information requested by OHRE, if applicable.

3.2.3.6 If the report cannot be completed in its entirety within the required time period, the report should describe what information is still needed and when the investigator anticipates that a follow-up report will be submitted.
3.2.4 Root Cause Analysis

Root cause analysis (RCA) is a class of problem solving methods used to identify the root causes of problems or events. For systemic problems, there may be multiple causes that require different actions. It may be relevant to perform an RCA so that appropriate corrective actions can be implemented to address the various contributing causes. Some corrective actions may require involvement of the institution (e.g., provisions of additional administrative support for the research team/activities).

3.2.4.1 Questions to ask to identify root causes:
- What was the error?
- How did it occur?
- How widespread?
- Why did it occur? Keep asking "why" until you identify root cause.

3.2.5 Corrective and Preventive Action (CAPA) Plans

Corrective actions are those taken to act on a problem that has already occurred. Preventive actions are those actions taken to eliminate the root cause of a potential problem. When reviewing a report of a UPIRSO, Serious Noncompliance, Continuing Noncompliance, Suspension or Termination of IRB approval, the HHS Office of Human Research Protections (OHRP) assesses most closely the adequacy of the actions taken by the institution to address the problem. In particular, OHRP assesses whether or not the corrective and preventative actions will help ensure that the incident will not happen again with the investigator or protocol in question, with any other investigator or protocol, or with the IRB. Therefore, OHRP recommends that, when appropriate, corrective actions be applied institution-wide. The FDA indicates that corrective and preventive actions are absolutely necessary to resolve problems and noncompliance in research. Although investigators have implemented CAPAs for decades, it is now an expectation that CAPAs are thoroughly documented, implemented, and evaluated over time for effectiveness, if appropriate.

3.2.5.1 CAPAs should include:
1. Description of the corrective and preventative actions taken or planned by the study team.
2. Date(s) on which the action(s) were taken or are planned.
3. The personnel who are responsible for the implementation the actions. The CAPA should describe whether different individuals are responsible for different actions.
4. If applicable, any plan/procedure to evaluate the implementation of the CAPA, personnel who are responsible for the evaluation, and the timeframe for the evaluation.

3.2.5.2 Documentation of CAPA. Suggested format:
1. Action type (corrective or preventive)
2. Action description
3. Responsible party
4. Due date
5. Plan for effectiveness check
6. Outcome of effectiveness check
7. If applicable, amendments to the CAPA

3.2.5.3 The IRB will make the final determination regarding the sufficiency of the CAPA.

3.2.6 Submission of Follow-up Report
Follow-up reports can be submitted any time during review or once a report has been resolved. An additional report to the IRB should be submitted if and when the CAPA has been evaluated for effectiveness. Reports will be screened by the OHRE Compliance Manager. Management of “New Safety Information” is described in SOP 1402.

3.3 External Adverse Event Reports
It is neither useful nor necessary under the regulations for reports of individual adverse events occurring in subjects enrolled in multicenter studies to be distributed routinely to investigators or IRBs at all institutions conducting the research. In general, the investigators and IRBs at all these institutions are not appropriately situated to assess the significance of individual external adverse events. Individual adverse events should only be reported to investigators and IRBs at all institutions when a determination has been made that the events meet the criteria for a UPIRSO. Ideally, adverse events occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/DMC) in accordance with a monitoring plan described in the IRB-approved protocol.

3.3.1 IND/IDE Safety Reports
The UNC IRB does not accept sponsor IND/IDE safety reports describing adverse events that have occurred at sites for which the UNC IRB does not have oversight responsibility unless the report is of an incident that is (1) unexpected, (2) related or possibly related to participation in the research, (3) serious or suggests that there are new or increased risk to subjects, and (4) warrants a change to the protocol or consent or subject notification. IND/IDE Safety Reports are submitted promptly as New Safety Information and must include an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents a UPIRSO. Changes to the research are submitted as a modification.
4 DEFINITIONS

4.1 IND Safety Report: A written report from a sponsor to the FDA of any adverse event associated with the use of the drug that was both serious and unexpected, or other adverse event or safety finding based on pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies that suggest a significant risk for human subjects and would cause the sponsor to modify the protocol-related documents or prompt other action to ensure the protection of human subjects.

4.2 Adverse event (AE): Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research. Adverse events encompass both physical and psychological harms and occur most frequently in the context of biomedical research, although they can occur in the context of social and behavioral research.

4.3 Internal adverse event: Adverse events experienced by subjects at sites that are relying on the UNC IRB for review of the research. In the case of an internal adverse event the principal investigator typically becomes aware of the adverse event directly from the subject, co-investigator or other member of the study staff, or the subject’s healthcare provider.

4.4 External adverse event: Adverse events experienced by subjects enrolled at sites that are not relying on the UNC for IRB review of the research. In the case of an external adverse event, the principal investigator typically becomes aware of the adverse event upon receipt of a report from the sponsor, coordinating center or other monitoring group, such as a Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC), or collaborating investigator at another site.

4.5 Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO): Any incident, experience, or outcome that

4.5.1 is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

4.5.2 is related or possibly related to a participant’s participation in the research; and

4.5.3 is serious or suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

4.6 Unexpected adverse event: Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is not consistent with either:

4.6.1 the known or foreseeable risk of adverse events associated with the procedures involved in the research that are 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) other relevant sources of information, such as product labeling and package inserts; or

4.6.2 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.

4.7 Related to the research: An incident, experience or outcome that is likely to have resulted from participation in the research study.

4.8 Possibly related to the research: The reasonable possibility that the adverse event, incident, experience or outcome may have been associated with the procedures involved in the research (modified from the definition of associated with use of the drug in FDA regulations at 21 CFR 312.32(a)). Reasonable possibility means that the event is more likely than not related to participation in the research or, in other words, there is a >50% likelihood that the event is related to the research procedures.

4.9 Serious adverse event means any event temporally associated with the subject’s participation in research that meets any of the following criteria:

4.9.1 results in death;
4.9.2 is life threatening (places the subject at immediate risk of death from the event as it occurred);
4.9.3 requires inpatient hospitalization or prolongation of existing hospitalization;
4.9.4 results in a persistent or significant disability/incapacity;
4.9.5 results in a congenital anomaly/birth defect; or
4.9.6 any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include 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).

4.10 Unanticipated Adverse Medical Device Effect: Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a medical device (if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the materials reviewed by the IRB); or, any other unanticipated serious problem associated with a medical device that relates to the rights, safety, or welfare of participants.

4.11 Protocol deviation: A variance from the approved study protocol. (Note: the term ‘protocol deviation that harmed subject(s) or others or placed subject(s) or others at increased risk of harm’ has replaced the term ‘protocol violation’).

4.12 Breach of Privacy: Privacy is the state of being free from the observation, intrusion, or attention of others. A breach of privacy in the context of human subjects research occurs when there is a failure to provide participants with the privacy protections described in the consent document. Breach of confidentiality: In the context of human subjects research, confidentiality is the condition that results when data are
maintained in a way that prevents inadvertent or inappropriate disclosure of participants’ identifiable information. A breach of confidentiality occurs when a participant’s private information is disclosed to a third party without his or her consent.

4.13 Noncompliance: Intentional or unintentional failure to follow applicable federal regulations, the requirements or determinations of the IRB, the IRB-approved study protocol, or University policies. Can occur as a result of performing an act(s) that violate(s) requirements. Can also occur as a result of failing to act when required.

4.14 Allegation of Noncompliance: An unproven assertion of “Noncompliance” by a subject or a third party.

4.15 Continuing Noncompliance: Any “Noncompliance” that occurs after implementation of an IRB-approved CAPA plan that is due to the failure of the investigator and/or research team to comply with that CAPA plan OR repeated instances of noncompliance within one study or across multiple studies that has a high likelihood of resulting in Serious Noncompliance.

4.16 Serious Noncompliance: “Noncompliance” that adversely and significantly affects the rights or welfare of participants.

4.17 Rights: The entitlement of human subjects for adequate protections based on the ethical principles and regulations underpinning human subjects research.

4.18 Welfare: A state of physical, psychological, social, economic and legal well-being.

4.19 Suspension: Temporary withdrawal of approval by the IRB of some or all research activities associated with a study. Research activities may include, but are not limited to the following: recruitment, screening/enrollment, research intervention/interaction, follow-up. IRB approval may be suspended by either the Chair or the convened IRB. Suspended research remains under the jurisdiction of the IRB and is subject to continuing review.

4.20 Termination: Permanent withdrawal of IRB approval of all research activities associated with a study. IRB approval may only be terminated by the convened IRB. Terminated research is no longer subject to continuing review.

5 REFERENCES

5.1 DHHS Regulations: 45 CFR 46.103(b), 45 CFR 46.103(b)(4)(iii), 45 CFR 46.103(b)(5)

5.2 FDA Regulations: 21 CFR 56.103(a), 21 CFR 56.108(a)(3)

5.3 OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007

5.4 FDA Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection, January 2009

5.5 FDA Guidance for Industry and Investigators — Safety Reporting Requirements for INDs and BA/BE Studies, December 2012

6 RELATED DOCUMENTS

6.1 SUPPLEMENT 1, Examples of New Safety Information

6.2 SOP 1402, Management of New Safety Information
SUPPLEMENT 1: Examples of New Safety Information

Examples of an Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO; any incident, experience, or outcome that is (a) unexpected (in terms of nature, severity, or frequency); related or possibly related to a participant’s participation in the research; and serious or otherwise one that suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized):

1. A participant with chronic gastroesophageal reflux disease enrolls in a phase 3 clinical trial at UNC evaluating a new investigational agent that blocks acid release in the stomach. Two weeks after starting study intervention the participant is hospitalized with acute kidney failure as a result of rhabdomyolysis. The known risk profile of the investigational agent does not include rhabdomyolysis, and the IRB-approved protocol and informed consent document for the study does not identify kidney damage as a risk of the research. Evaluation of the participant reveals no other obvious cause for rhabdomyolysis. The UNC principal investigator reported the event to the Sponsor as possibly related. The sponsor agreed with the investigator’s assessment of the event and notified the FDA and all participating investigators in an IND Safety Report. This is an example of a single, uncommon adverse event, known to be strongly associated with drug exposure. The adverse event meets the criteria for a UPIRSO because it is (a) unexpected in nature, (b) possibly related to the research, and (c) serious.

2. Participants with coronary artery disease presenting with unstable angina are enrolled in a multicenter clinical trial evaluating the safety and efficacy of an investigational vascular stent. Based on prior studies in animals and humans, the investigators anticipate that up to 5% of participants receiving the investigational stent will require emergency coronary artery bypass graft (CABG) surgery because of acute blockage of the stent that is unresponsive to non-surgical interventions. The risk of needing emergency CABG surgery is described in the IRB-approved protocol and informed consent document. After the first 20 participants are enrolled in the study, a DSMB conducts an interim analysis, as required by the IRB-approved protocol, and notes that 10 participants have needed to undergo emergency CABG surgery soon after placement of the investigational stent. The DSMB monitoring the clinical trial concludes that the rate at which participants have needed to undergo CABG greatly exceeds the expected rate and communicates this information to the sponsor and all investigators on the trial. The sponsor evaluates the information and concludes that the information represents an Unanticipated Adverse Device Effect (UADE). Consequently, the sponsor reports an analysis of the events to FDA and to all study investigators. The UADE meets the criteria for UPIRSO because (a) the frequency at which participants have needed to undergo emergency CABG surgery was significantly higher than the expected frequency; (b) these events were related to participation in the research; and (c) these events were serious.

3. Participants with essential hypertension are enrolled in a phase 2, non-randomized multicenter clinical trial testing a new investigational antihypertensive drug. At the time the clinical trial is
4. A behavioral researcher at UNC conducts a study in college students that involves completion of a detailed survey asking questions about early childhood experiences. During the completion of the survey, one student participant experiences intense sadness and depressed mood that resolved without intervention after a few hours. The protocol and informed consent document for the research did not describe any risk of such negative psychological reactions. Upon further evaluation, the investigator determines that the participant’s negative psychological reaction resulted from certain survey questions that triggered repressed memories of physical abuse as a child. The investigator had not expected that such reactions would be triggered by the survey questions. This is an example of a non-serious, internal adverse event that meets the criteria for a UPIRSO because it is (a) unexpected in nature, (b) related to the research, and (c) suggests that the research placed subjects at a greater risk of psychological harm than was previously known or recognized.

5. An investigator at UNC conducting behavioral research collects individually identifiable sensitive information about sexual behaviors by surveying college students. The data are stored on a laptop computer without encryption (encryption is required by the protocol), and the laptop computer is stolen from the investigator’s car on the way home from work. The laptop was not recovered. This is an example of a breach of confidentiality as well as a protocol deviation that harmed a participant; it meets the criteria for a UPIRSO because the loss of the laptop was (a) unexpected (i.e., the investigators did not anticipate the theft); (b) related to participation in the research; and (c) placed the participants at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.

6. During a routine monitoring visit by the sponsor, it is discovered that two consent documents are missing. The consent documents contain the participants’ names and indicate that the participants were in a study concerning illicit drug use. Informed consent was obtained in the ABC hospital by a study coordinator and the signed consent form was possibly lost during transit to the study coordinator’s office, which is located in a different building on the ABC campus. Despite an extensive
search of the file cabinets in the office and the clinic area, the forms were not found. This is an example of a potential breach of confidentiality that meets the criteria for a UPIRSO because it was (a) unexpected; (b) related to participation in the research; and (c) placed the participants at a greater risk of psychological, social, and economic harm than was previously known or recognized. Although the risk of a breach may be described in general terms in an informed consent document, a specific incidence of breach/ potential breach of confidentiality is considered ‘unexpected’. Because the documents were transported from one building on campus to another, there is a possibility that the documents were lost in transit and that a participant’s status as an illicit drug user was inadvertently disclosed to individuals outside the research team.

7. A participant receives a dose of an experimental agent that is 10-times higher than the dose dictated by the IRB-approved protocol. Although the participant experienced no detectable harm or adverse effect after an appropriate period of careful observation, the dosing error increased the risk of toxic manifestations of the experimental agent. This is an example of a protocol deviation that placed a participant at increased risk of physical harm. The incident meets the criteria for a UPIRSO because it was (a) unexpected; (b) related to participation in the research; and (c) placed the participants at a greater risk of physical harm than was previously known or recognized.

8. A blood test that is needed to monitor participant safety during the trial is missed for a participant participating in a phase 3, randomized, double-blind controlled clinical trial comparing the relative safety and efficacy of a new chemotherapy regimen. As a result, grade 3 neutropenia is not detected until the next study visit. The protocol stipulates a reduction in dosage if > grade 3 neutropenia occurs. This is an example of a protocol deviation that harmed a participant. The deviation meets the criteria for a UPIRSO because it was (a) unexpected; (b) related to participation in the research; and (c) placed the participants at a greater risk of physical harm than was previously known or recognized.

Examples of noncompliance (Failure to follow applicable federal regulations, the requirements or determinations of the IRB, provisions of the IRB approved research study, or University policies. The failure can occur as a result of performing an act(s) that violate(s) requirements or as a result of not acting when required to do so):

1. An investigator receives notification that the IRB has reviewed his/her research application but requires minor revisions before the study can be approved. The investigator submits the study revisions, as stipulated, but proceeds to enroll research participants prior to receiving final IRB approval.

2. An investigator neglects to submit the annual progress report and request for continuing review and the study’s approval expires. After the expiration date, the investigator enrolls new participants and/or continues to interact with currently-enrolled participants to collect additional data.

3. Failure to obtain informed consent or deviating from the informed consent or recruitment process as described in the IRB approved protocol. For example, a student volunteer who has not completed
human participants research ethics training conducts the consent process; or, a researcher recruits and enrolls participants directly from among students enrolled in his/her class without having declared this approach as part of the recruitment plan that was approved by the IRB.

4. The consent form is revised to describe liver injury at a higher frequency than previously stated in the original consent form. The investigator enrolls several new participants using the outdated form, thereby failing to provide a participant with new information about procedures or risks that may affect the participant’s willingness to continue/participate in the study.

5. After the first wave of focus group data collection, the investigator revises the focus group guide including new questions about illicit drug use that probe more deeply than the questions previously approved by the IRB. Similar problems may arise regarding the use of unapproved materials such as fact or information sheets, recruitment materials, questionnaires, scripts or other materials provided to participants.

6. A new researcher who has completed Good Clinical Practice (GCP) training but not human subjects protection training, performs a routine physical examination for a research participant. Failure to complete IRB- or institutionally-required human subjects protection training prior to engaging in human subjects research constitutes noncompliance.

7. A phase1 drug trial is approved to enroll 12 participants. At annual renewal, the investigator reports that more than 12 participants completed the study. Over enrollment of participants constitutes noncompliance.

When noncompliance has occurred, federal regulations require the IRB to determine whether the incident is serious, continuing or both.

**Examples of Serious Noncompliance** (“Noncompliance” that adversely and significantly affects the rights or welfare of participants):

1. A participant with diabetes is randomized to receive a medication designed to lower blood glucose. The investigational pharmacy misinterprets the physician’s order and provides study medication at a dosage level 70% below what is described in the approved protocol. Two weeks into treatment the participant lapses into a diabetic coma and requires emergency treatment. This is an example of a protocol deviation that placed a participant at increased risk of physical harm. The incident meets the criteria for Serious Noncompliance because the participant’s welfare was adversely and significantly affected. It is also a UPIRSO.

2. In order to locate a participant for follow-up, the researcher faxes the participant’s name on the study letterhead to the HR department of the participant’s current employer. The title of the study is on the letterhead and conveys sensitive information about HIV status. At intake, the participant identified several individuals that the researchers may contact for updated contact information at the time of follow-up if the participant cannot otherwise be reached. The employer was not listed as contact, but the investigator knew the participant’s place of work. Upon receipt of the letter, an HR
representative from the participant’s employer notified the UNC IRB. This is an example of a breach of confidentiality and a protocol deviation that places participants at increased risk of harm. The incident meets the criteria for Serious Noncompliance because the participant’s rights (in this case, privacy and confidentiality) were adversely and significantly affected. It is also a UPIRSO.

3. The IRB learns of a project that involved retrospective review of patients’ clinical data to examine the efficacy of a certain genetic testing process. The study team should have sought IRB approval prior to starting the project because the project involves a systematic investigation designed to contribute to generalizable knowledge and acquisition of private identifiable information (i.e., it constitutes human subjects research). This is an example of conducting research without approval. It meets the criteria for Serious Noncompliance because conducting research without approval adversely and significantly impacts the participants’ right to privacy. It also represents a UPIRSO.

4. During an internal audit it is discovered that the fifth participant enrolled in a phase I, open-label, uncontrolled clinical study evaluating the safety and efficacy of an investigational study drug is taking an excluded concomitant medication that may interfere with the metabolism of the study drug and increase the levels of study drug in the body. The participant had disclosed that he was taking the concomitant drug at screening, but the study physician missed this important information during the eligibility review. The participant was enrolled despite taking the excluded drug. After taking study drug for two weeks, the participant is hospitalized with symptoms of liver dysfunction. Evaluation of the participant reveals no other obvious cause for liver dysfunction. This is an example of a deviation that harmed participants. The deviation meets criteria for Serious Noncompliance because treating the participant while he/she was taking the excluded medication adversely and significantly impacted the participant’s the rights and welfare. It also represents a UPIRSO.

5. An investigator is evaluating the efficacy of cognitive training in adults with Alzheimer disease. Eager to meet the target enrollment number, the investigator sends a recruitment email not approved by the IRB to a public listserv that implies that the cognitive training will produce improvements in general cognition and in quality of life and well-being. The investigator also increased the monetary incentive from $100 to $1000. This a deviation that placed participants or others at increased risk of psychological harm. The deviation meets criteria for Serious Noncompliance because (1) offering an undue inducement to participate and (2) implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the protocol adversely and significantly impacts the rights and welfare of potential participants. It also represents a UPIRSO.

6. An industry Sponsor revises the investigator brochure, master protocol, and consent form to reflect a new risk associated with the study drug. Rather than submitting these new materials to the IRB promptly, per the New Safety Information reporting SOPs, the investigator submits them at annual renewal 7 months later. This noncompliance meets the criteria for Serious Noncompliance because not reporting new safety information adversely and significantly impacts the participants’ right to receive new information that may influence their willingness to continue to participate in the study. It also represents a UPIRSO.
7. A participant with seizures enrolls in a randomized, phase 3 clinical trial comparing a new investigational anti-seizure agent to a standard, FDA-approved anti-seizure medication. Two months into the study, the sponsor increases the time of birth control use after the last dose of anti-seizure agent from 8 weeks to 16 weeks. This change was implemented following the analysis of new data from a different trial indicating the investigational agent remains in the body longer than expected and can have adverse effects on a fetus. Three women of child bearing potential are not reconsented with this information, and one of the women becomes pregnant 10 weeks after the last dose of study medication. Upon learning about the error, the woman is very distressed and immediately withdraws from the study. The failure to reconsent participants with the new safety information adversely and significantly impacted the participants’ rights (i.e., to receive new safety information) and welfare. It also meets the criteria for a UPIRSO.

8. A research protocol is IRB approved for enrollment of clinic patients for the collection of blood samples to be available for future research to isolate unknown genetic markers and develop novel gene therapies. The IRB approved consent and protocol specify that only adults may be enrolled. In the PI’s clinic, many patients under 18 also present for treatments and blood is routinely drawn from them for clinical purposes. The PI decides to expand the cohort to include minors (ages 15-17), as there is minimal risk and the future studies could yield therapies for younger members of the cohort who could potentially benefit from decreased morbidity and mortality. The PI does not notify the IRB or request permission from the parents, however he does assent minor participants using the consent document approved for adults. Deviating from the IRB approved consent process and failing to obtain parental permission adversely and significantly impacted the participants’ right for human subjects research protection under the law. It also represents a UPIRSO.

**Examples of Continuing Noncompliance** (Any “Noncompliance” that occurs after implementation of an IRB-approved CAPA plan that is due to the failure of the investigator and/or research team to comply with that CAPA plan OR repeated instances of noncompliance within one study or across multiple studies that has a high likelihood of resulting in Serious Noncompliance):

1. Multiple instances of not performing protocol-driven laboratory tests that are needed to monitor participant welfare and safety.

2. Repeated failure to respond to IRB inquiries or requests for documentation.

3. Multiple instances of an investigator using unapproved documents.

4. Failure to follow a directive or CAPA established by the IRB.
1 PURPOSE
1.1 This SOP establishes written procedures for ensuring prompt review and reporting of any Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO), Serious Noncompliance, Continuing Noncompliance, Suspension or Termination of IRB approval in accordance with 45 CFR 46.103(a) and (b)(5), and 21 CFR 56.108(b).
1.2 This SOP begins when the UNC Office of Human Research Ethics (OHRE) receives a New Safety Information (NSI) submission.
1.3 This SOP ends when the Principal Investigator (PI), and if applicable, the Institutional Official (IO) and designee, and Federal Regulatory Agencies have been notified of the outcome of the NSI review.

2 RESPONSIBILITY
2.1 The convened IRB; the Safety Welfare Analysis Group (SWAG); the IO and designee; the IRB Chair, Co-Chairs, and Vice-Chairs; OHRE leadership; and the Safety/Compliance team are responsible for carrying out the procedures described in this SOP.

3 PROCEDURES
3.1 NSI Triage
Upon receipt of NSI, the OHRE Safety/Compliance team in consultation with OHRE leadership will promptly triage the NSI.
3.1.1 NSI that suggests that participants or others may be at risk of imminent serious harm is triaged to an IRB Chair, Co-Chair or Vice-Chair. The OHRE Director is also notified.
3.1.2 All other NSI is referred to SWAG.
3.1.3 Information that does not represent NSI is resolved or re-triaged within the IRB.

3.2 Interim Suspension
The IRB Chair(s) will review the referred NSI. If it is determined that participants may be at risk of imminent serious harm, the IRB Chair, Co-Chair or Vice-Chair will
3.2.1 Initiate an interim suspension of IRB approval of all activities or a subset of activities.
3.2.2 Refer the interim suspension and associated NSI for review by the convened IRB. An interim suspension must be reviewed by the convened IRB to either uphold or lift the suspension.
3.2.3 Notify the PI and designated personnel, the IRB Chair or Co-Chair of the IRB that will review the interim suspension, and OHRE leadership.

3.3 SWAG NSI Review
SWAG, a group of two or more individuals with expertise in clinical research and an IRB Chair, Co-Chair or Vice-Chair, reviews NSI and proposed Corrective and Preventative (CAPA) plans and conducts fact-finding.
3.3.1 If the NSI suggests that participants or others may be at risk of imminent serious harm, SWAG will:
3.3.1.1 Initiate an interim suspension of IRB approval of all activities or a subset of activities.
3.3.1.2 Refer the interim suspension and associated NSI for review by the convened IRB. An interim suspension must be reviewed by the convened IRB to either uphold or lift the suspension.

3.3.1.3 Notify the PI and designated personnel, the IRB Chair or Co-Chair of the IRB that will review the interim suspension, and OHRE leadership.

3.3.2 If the NSI may represent an Unanticipated Problem Involving Risks to Subjects or Others (UPIRSO), Serious Noncompliance, or Continuing Noncompliance, SWAG will:

3.3.2.1 Refer the NSI to the convened IRB for review.

3.3.2.2 Notify the PI and designated personnel, and the IRB Chair(s) of the IRB that will be assigned the NSI.

3.3.3 If the NSI represents Noncompliance or other information that is not an UPIRSO, Serious Noncompliance, or Continuing Noncompliance, SWAG will:

3.3.3.1 Work with the PI to ensure that the proposed CAPA plan is appropriate.

3.3.3.2 Notify the PI and designated personnel of the determination and the approved CAPA.

3.3.3.2.1 If Minor Noncompliance, notify the PI and designated personnel to document the Minor Noncompliance in the research record (i.e. deviation log) and implement a CAPA plan that addresses the root cause of the Minor Noncompliance.

3.3.3.2.2 Provide education on reporting requirements.

3.3.4 If the reported information is not NSI, SWAG will:

3.3.4.1 Notify the PI and designated personnel

3.3.4.2 Provide education on reporting requirements

3.3.5 If SWAG is uncertain about what the reported information represents, it will refer the information to the convened IRB for review.

3.3.6 If the NSI is applicable to other UNC parties (e.g. University Counsel, UNC Hospitals Risk Management, Research Integrity Officer, Privacy Office), SWAG will notify the appropriate parties.

3.4 NSI Review by the Convened IRB

The convened IRB serves in accordance with 45 CFR 46, and 21 CFR 50 and 56 (See SOP 401 for more information about the function of the convened IRB). NSI Review follows the same processes as outlined in SOP 701, in addition to the following:

3.4.1 NSI referred to the IRB and any supporting documentation will be distributed to IRB Chair(s) and members for review approximately 7 calendar days prior to the date of the convened meeting.

3.4.2 The PI and study team may be invited to participate to answer questions or to clarify information.

3.4.3 The IRB will use a review worksheet to guide the NSI discussion.

3.4.4 The IRB support personnel will document the NSI review, including discussion, controverted issues, determinations, the approved CAPA plan, stipulations, motions and votes.

3.4.5 Following NSI Review, the Safety/Compliance team will notify the PI of the outcome of the review.

3.4.5.1 The PI notification will include the IRB’s determination, including the rationale for the determination, the approved CAPA plan, stipulations and any other information as directed by the Board.

- Copy to: IO and designee, the IRB Chair/Co-Chair, OHRE leadership, and other relevant parties at the discretion of the IO and designee, and Director of OHRE if the NSI is determined to constitute an UPIRSO, Serious Noncompliance, Continuing Noncompliance, a Suspension or Termination of IRB Approval.
3.5 Notification of Federal Agencies

3.5.1 Federal regulations require that the IRB follow written procedures for ensuring prompt reporting of any UPIRSO, Serious Noncompliance, Continuing Noncompliance, Suspension or Termination of IRB Approval to the appropriate federal agencies. The appropriate federal agency is:

- The Department of Health and Human Services (HHS), Office of Human Research Protections (OHRP), when research is federally funded.
- The Food and Drug Administration (FDA), when the research is FDA-regulated.
- Other federal agencies, when the research is overseen by those agencies and they require reporting separate from OHRP.

3.5.2 The Safety/Compliance team in collaboration with the Chair/Co-Chair and OHRE leadership will:

3.5.2.1 Prepare a report that includes:
- Title of the study;
- Name of the PI;
- IRB Study number;
- The number of any applicable federal award(s) (grant, contract, or cooperative agreement);
- IND or IDE number;
- A detailed description of the NSI;
- The reason for the suspension or termination of IRB approval, as applicable.
- A CAPA plan that addresses the root cause of the NSI. Of note, when reviewing a report of a UPIRSO, Serious Noncompliance, Continuing Noncompliance, Suspension or Termination of IRB approval, OHRP assesses most closely the adequacy of the actions taken by the institution to address the problem. Specifically, OHRP assesses whether the CAPA plan will ensure that the incident will not happen again with the investigator or protocol in question, with any other investigator or protocol, or with the IRB. Therefore, OHRP recommends that, when appropriate, the CAPA plan be applied institution wide.
- Copy to: IO and designee, Director of OHRE, IRB Chairs, PI, Office of University Counsel, Office of Clinical Trials, Office of Sponsored Research
- Copy to: PI’s Department Chair, Division Chair, Director, and/or Dean, if the NSI represents Serious Noncompliance, Continuing Noncompliance, a Suspension of IRB Approval, or a Termination of IRB Approval.
- Copy to: Other relevant parties at the discretion of the IO and designee and Director of OHRE.

3.5.2.2 Send the draft report to the PI for review of the study description and event details.

3.5.2.3 If UNC is the reviewing IRB for another institution, and the NSI involves researchers or participants at that institution, provide the relying institution a reasonable opportunity to review and comment on the report.

3.5.2.4 Send draft report to the IO and designee for review and approval.
3.5.2.5 Typically, send the report within 30 days of suspension or termination of approval, or within 30 days of identifying an event as meeting the criteria for an Unanticipated Problem Involving Risks to Subjects or Others, Serious Noncompliance, or Continuing Noncompliance.

3.5.2.6 The report is described as a preliminary report when it concerns an UPIRSO, Serious Noncompliance, or Continuing Noncompliance for which information is still being gathered, or for which proposed corrective and preventative actions have not yet been approved by the convened IRB.

3.5.2.6.1 The final (i.e., follow-up) report is sent within 30 days of final resolution.

3.5.3 The Safety/Compliance team, IRB Chair/Co-Chair, OHRE leadership and the IO will review all responses received from Federal Agencies. All correspondence will be maintained on file in the OHRE.

3.5.4 Reports to funding agencies (e.g., NIH) will be sent under separate cover by the IO or designee.

3.6 Notification of the Association for the Accreditation of Human Research Protection Programs (AAHRPP)

3.6.1 AAHRP requires notification of the following information, generally within 48 hours after the institution or researchers become aware of the information:

3.6.1.1 Any negative actions by a government oversight office, including, but not limited to, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated, FDA Restrictions on Investigators, and any corresponding compliance actions taken under non-US authorities related to human research protections.

3.6.1.2 Any litigation, arbitration, or settlements initiated related to human research protections.

3.6.1.3 Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding human subjects research conducted at or by UNC-CH or about UNC-CH’s Human Research Protection Program (HRPP).

3.6.2 Information received by OHRE outside of IRBIS is triaged to the Safety/Compliance team and OHRE leadership.

3.6.3 The Safety/Compliance team and OHRE leadership will notify AAHRPP without delay.

3.7 Reconsideration
As required by regulations, any decision of the IRB with respect to research involving human subjects is final. However, the PI may request that the convened IRB reconsider its determination and/or CAPA plan based on new information that was not available or considered at the time the determination was made. No other circumstances warrant a reconsideration. The petition must be made within 10 calendar days of notification of the IRB’s findings. At the IRB’s discretion, the PI may be invited to the IRB meeting at which his or her petition will be considered.

3.8 Participant or Third-Party Complaint or Allegation of Noncompliance

3.8.1 Participants are encouraged to ask questions or voice any concerns or complaints they may have about the research. The PI is responsible for answering all questions, addressing all concerns, and responding to all complaints raised by participants to the best of his/her ability. The name and contact information of the PI responsible for the conduct of the research is required in all UNC consent documents.

3.8.2 Participants are also encouraged to discuss their rights or to voice their concerns or complaints about the research with OHRE. The telephone number and email of the OHRE is required in all UNC consent documents. OHRE contact information is also available to participants and third parties on the OHRE website.
3.8.3 When the UNC IRB waives the requirement for the PI to obtain a signed consent document, contact information for the PI is included in a study information sheet or other written information about the research.

3.8.3.1 Complaints received by the PI or study personnel:

3.8.3.1.1 The PI is responsible for ensuring that complaints are reviewed thoroughly and respectfully. Participants should not be penalized or lose any benefits they are receiving or have a right to receive as a result of the complaint.

3.8.3.1.2 The PI will address the complaint promptly and communicate its resolution to the complainant, generally within 30 days.

3.8.3.1.3 The PI must document all complaints received from participants or third parties and their resolution.

3.8.3.1.4 If the complaint meets NSI reporting requirement per SOP 1401, an NSI submission is required.

3.8.3.1.5 The PI and the study team will work with OHRE to resolve complaints.

3.8.3.2 Complaints received by OHRE:

3.8.3.2.1 The Safety/Compliance team reviews all complaints with consultation by the OHRE leadership and the IRB Chair(s) as applicable. OHRE will maintain privacy of the complainant where privacy is a concern or when requested by the complainant.

3.8.3.2.2 Complaints received outside of IRBIS, regardless of point of origin, are recorded in writing and provided to the Safety/Compliance Manager.

3.8.3.2.3 The Safety/Compliance team will notify the PI of the complaint.

3.8.3.2.3.1 If the complaint meets the criteria for NSI, an NSI submission with a response to the complaint is required. The NSI submission will be reviewed as described in this SOP.

3.8.3.2.3.2 Complaints regarding minor administrative issues such as a brief delay in compensation does not require an NSI submission. Upon resolution of a minor administrative complaint, the PI is required to summarize the response to the complaint in an email to the Safety/Compliance Manager.

3.8.3.2.4 The OHRE Safety/Compliance team will work with the PI, the IRB Chair(s) and OHRE leadership to resolve the complaint, and will communicate its resolution to the complainant, generally within 30 days of receipt of the complaint.

3.8.3.2.5 OHRE will maintain records of complaints and their resolution, and a copy will be retained in the applicable protocol file.

3.9 NSI Review when UNC is Ceding IRB Review

If UNC is ceding review and oversight to another IRB and that IRB has made a regulatory determination of Serious Noncompliance, Continuing Noncompliance, an Unanticipated Problem Involving Risks to Subjects or Others that involve UNC participants or researchers, the determination and the approved CAPA is reportable as NSI (see SOP 1401).

3.9.1 SWAG will:

3.9.1.1 Review the CAPA plan to ensure that it appropriately addresses the event.
3.9.1.1 If the CAPA is determined to be inadequate, SWAG will refer the NSI and SWAG’s findings to the convened IRB.

3.9.1.2 If the CAPA is deemed adequate, confirm that the CAPA plan has been implemented at UNC.

3.9.1.3 Request update on participants and others that may have been harmed.

3.9.1.4 If not previously received, request a copy of the notification letter to Federal Agencies, as applicable.

3.9.2 The convened IRB will:

3.9.2.1 Review the NSI, the approved CAPA plan and SWAG’s findings, and propose updates to the CAPA plan as applicable.

3.9.2.2 Notify the IRB of record and the UNC IO and designee of the UNC IRB’s findings and proposed CAPA plan.

4 DEFINITIONS

4.1 Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO): Any incident, experience, or outcome that

4.1.1 Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

4.1.2 Is related or possibly related to a participant’s participation in the research; and

4.1.3 Is serious or suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

4.2 Allegation of Noncompliance: An unproven assertion of “Noncompliance” by a participant or a third party.

4.3 Noncompliance: Intentional or unintentional failure to follow applicable federal regulations, the requirements or determinations of the IRB, provisions of the IRB approved study protocol, or University policies. Can occur as a result of performing an act(s) that violate(s) requirements. Can also occur as a result of failing to act when required.

4.4 Minor Noncompliance: Any “Noncompliance” that does not (1) suggest that the research placed participants or others at increased risk of harm, (2) and adversely affects the safety, rights, or welfare of participants; and/or (3) and adversely affects the integrity of the research. (2) does not adversely affect subjects’ rights or welfare.

4.5 Continuing Noncompliance: Any “Noncompliance” that occurs after implementation of an IRB approved corrective action plan that is due to the failure of the investigator and/or research team to comply with that corrective action plan; OR, repeated instances of noncompliance, within one study or across multiple studies, that has a high likelihood of resulting in Serious Noncompliance.

4.6 Serious Noncompliance: “Noncompliance” that adversely and significantly affects the rights or welfare of participants.

4.7 Suspension: Temporary withdrawal of approval by the IRB of some or all research activities associated with a study. The convened IRB can suspend approval of research that is (1) not being conducted in accordance with the IRB’s requirements or (2) has been associated with unexpected serious harm to subjects. Suspended research remains under the jurisdiction of the IRB and is subject to continuing review.

4.8 Termination: Permanent withdrawal of approval by the IRB of all research activities associated with a study. The convened IRB can terminate approval of research that is (1) not being conducted in accordance with the IRB’s requirements or (2) has been associated with unexpected serious harm to subjects. IRB approval may only be terminated by the convened IRB.
5 REFERENCES

5.1 DHHS Regulations: 45 CFR 46.103(a) and (b)(5)
5.2 FDA Regulations: 21 CFR 56.108(b)
1 Purpose

Investigators are ultimately responsible for the conduct of research. Investigators may delegate tasks to appropriately trained and qualified members of their research team. However, investigators must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibilities.

2 Procedures

2.1 Investigators

The research team is made up of ‘investigators’, differentiated as follows, along with their responsibilities in the conduct of research involving human participants.

At the University of North Carolina at Chapel Hill (UNC-Chapel Hill) only faculty members with the UNC-Chapel Hill-paid appointments may serve as the Principal Investigator or as the faculty sponsor on a research project involving human subjects.

Adjunct faculty of the Organization and any investigator whose status is considered to be “in training” (e.g., students and medical residents) may not serve as a PI but may serve as a co-investigator or sub-investigator. PIs will ensure that research designed and conducted by trainees has sound research design and is appropriately supervised.

The IRB recognizes one PI for each study. The PI has ultimate responsibility for the research activities.

Studies that require expertise or skills beyond those held by the PI must either be modified or have expertise and skills supplemented by the inclusion of one or more additional qualified co/sub-investigators.

2.1.1 Trainee Investigators

Trainee investigators are students, employees in postdoctoral training programs, or fellows who have the primary research responsibility for an application submitted to the IRB. These investigators may take a leading role in the research, but do not have ultimate administrative and fiscal responsibility for the project. Trainee investigators should be privy to all correspondence sent by the IRB that pertains to a project on which a Trainee investigator is listed.
2.1.2 Sub-Investigators

A sub-investigator is any individual other than the PI who is involved in the conduct of a research study. Such involvement could include:

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

2.1.3 Research team members

Every member of the research team is responsible for protecting human subjects in accordance with the guidelines specified in SOP 101, reporting all noncompliance to the IRB, and for complying with all IRB findings, determinations and requirements. Team members must complete human subject research training as required by the University’s “Policy on Education and Certification of Investigators Involved in Human Subjects Research.”

2.2 Responsibilities

In order to satisfy the requirements of this policy, investigators who conduct research involving human subjects must:

1. Develop and conduct research that is in accordance with the ethical principles in the Belmont Report;
2. Develop a research plan that is scientifically sound and minimizes risk to the subjects;
3. Incorporate into the research plan a plan to ensure the just, fair, and equitable recruitment and selection of subjects;
4. When some or all of the subjects are likely to be vulnerable to coercion or undue influence (e.g., children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons), include additional safeguards in the study to protect the rights and welfare of these subjects;
5. Ensure that the research plan includes adequate provisions for the monitoring of subjects and data to ensure the safety of subjects;
6. Ensure that there are adequate provisions to protect the privacy interests of subjects;
7. Ensure that there are adequate provisions to protect data confidentiality and interests of subjects, including an information security plan that considers the collection, storage, maintenance, analysis, and transmission of data and other identifiable information;
8. Have sufficient resources necessary to protect human subjects, including:
   a. Access to a population that would allow recruitment of the required number of subjects.
   b. Sufficient time to conduct and complete the research.
   c. Adequate numbers of qualified staff.
   d. Adequate facilities.
   e. Necessary equipment.
   f. A plan to ensure proper supervision of the research including a plan for periods of absence or decreased availability.
   g. Availability of medical, psychological, or other support that subjects might require during or as a consequence of their participation in the research.

9. Assure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise qualified to perform such under the laws of North Carolina and the policies of the UNC-Chapel Hill.

10. Assure that all study personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based;

11. Assure that all persons assisting with the research are adequately trained and informed about the protocol/research plan and their specific duties and functions.

12. Promptly report any changes in, addition to, or departure of investigators or research staff to the IRB for evaluation and approval (note that investigators and staff may not begin work on the research until IRB-approved);

13. Protect the rights, safety, and welfare of participants;

14. Ensure that when private health information is used, legally effective HIPAA authorization is obtained for each subject unless the Privacy Board or IRB has approved a waiver of the requirement;

15. Ensure that the language in the consent form is consistent with that in the protocol/research plan and, when applicable, in the HIPAA authorization;

16. Obtain and document informed consent and ensure that no human subject is involved in the research prior to obtaining consent or consent/permission from their legally authorized representative, unless a waiver of the requirement has been approved by the IRB;

17. Have a procedure to receive questions, complaints, or requests for additional information from subjects and respond appropriately;

18. Ensure that all information provided to the IRB is accurate and complete so that the IRB may fulfill its responsibilities to review the research and make the required determinations;

19. Ensure that all research involving human subjects receives IRB review and approval in writing or a determination of exemption before research begins;
20. Ensure that all research involving human subjects is reviewed by other experts and organizational components and committees as applicable to the research;
21. Comply with all IRB decisions, conditions, and requirements;
22. Ensure that studies receive timely continuing IRB review and approval;
23. Report unanticipated problems, deviations, complaints, non-compliance, suspensions, terminations, and any other reportable events to the IRB;
24. Notify the IRB if information becomes available that suggests a change to the potential risks or benefits of the research
25. Obtain IRB review and approval before changes are made to the research unless a change is necessary eliminate apparent immediate hazards to the subject(s);
26. Seek HRPP or IRB assistance when in doubt about whether proposed research requires IRB review;
27. Retain records for the time period and in the manner required by applicable regulations, contractual agreements, and organizational policies.

Additional investigator responsibilities, including specific responsibilities for investigators engaged in FDA-regulated research are described elsewhere in this document.

2.3 Investigator Records

Under these policies investigators must maintain, at a minimum but not limited to, the following research records under these policies. In addition, investigators must also comply with all record-keeping sponsor requirements.

2.3.1 Study Records

- Individual subject records
- Recruitment materials
- Documentation of consent process (who, what, when and how)
- Signed consent forms
- Unanticipated Problem & Reportable Event Reports
- Subject complaint reports
- Results of all procedures conducted on the subject, including final visit (if no final visit, reason why: e.g., removal from study, withdrawal from study, death)

2.3.2 Regulatory Records

- Most recent IRB-approved protocol/research plan
- Previous versions of protocol/research plan
• All correspondence (i.e., approvals, reporting forms and responses, etc.) to and from the IRB
• All correspondence with the sponsor and others regarding the study
• Continuing review progress reports
• Modification Requests
• Investigational product accountability records, when applicable

2.3.3 Record Retention

Investigator records must be retained in accordance with regulatory, organizational and sponsor or grantor requirements, but no less than three years following the completion of the research. All records must be maintained securely with limited access. Disposal of investigator records must be done in such a manner that no identifying information can be linked to research data.

For records not included in the UNC-CH General Records Retention and Disposition Schedule, refer to Federal retention requirements

1. DHHS regulations require that, “records relating to research which is conducted shall be retained for at least 3 years after completion of the research.” [45 CFR 46.115(b)]

2. For Investigational New Drug (IND) research, the FDA requires that sponsors and investigators retain “records and reports required by this part for two years after a marketing application is approved for the drug; or if an application is not approved for drug, until two years after shipment and delivery of the drug for investigational use is discontinued and the FDA so notified.” [21 CFR 312.57(c)]

2.3.4 Public Records request

Some of this documentation may be subject to public access under the North Carolina Public Records Act. The Office of University Counsel should be consulted when a public records request is received.

A records retention and disposition schedule is a document used to identify and manage the records that document the activities and history of an organization. It identifies and classifies the records created, received, and used by the organization and provides instructions on how long they need to be retained for legal, fiscal, and historical purposes.

This records retention and disposition schedule is a tool for employees of The University of North Carolina at Chapel Hill to use when managing the records of the University. It lists records found in the administrative, academic, and health affairs units of the University and gives an assessment of their value by indicating if, and when, they should be destroyed or transferred to University Archives.
2.4 Recruitment Incentives

Payment arrangements among sponsors, organizations, investigators, and those referring research participants present a conflict of interest and may place participants at risk of coercion or undue influence or cause inequitable selection. Payment in exchange for referrals of prospective participants (“finder’s fees”) is not permitted. Similarly payments designed to accelerate recruitment that is tied to the rate or timing of enrollment (“bonus payments”) are also not permitted.

2.4.1 Compensation from Sponsors

To minimize inappropriate financial incentives in study sponsorship, project support in all University projects:

- Must be based on fair market value of services performed or actual cost;
- Must be expressly stated in a contract between the University and the research sponsor;
- May not be conditioned upon a particular research result or tied to successful research outcomes; and
- May not include payments or other incentives for achieving human subject enrollment target numbers or meeting target enrollment accrual timelines or identifying eligible human research subjects.

2.5 Investigator Concerns

Investigators who have concerns or suggestions regarding the UNC-Chapel Hill’s HRPP or IRB(s) should convey them to the Institutional Official or other responsible parties (e.g., supervisor, college dean, departmental Chair), when appropriate. The Institutional Official will consider the issue, and when deemed necessary, seek additional information and convene the parties involved to form a response for the investigator or make necessary procedural or policy modifications, as warranted. In addition, the Chair of the IRB or the OHRE Director will be available to address investigators’ questions, concerns and suggestions.

In addition to these SOPs, which are made available on the UNC-Chapel Hill website for investigators, investigators are also made aware of the process for expressing their concerns via statement on approval letters, link on the UNC-Chapel Hill website for concerns or complaints.
1 Purpose

It is the University of North Carolina at Chapel Hill (UNC-Chapel Hill) policy that any sponsored research conducted under the auspices of the Organization is conducted in accordance with federal guidelines and ethical standards.

The following describe the procedures required to ensure that all sponsored research meets this requirement.

2 Procedure

2.1 Definitions

Sponsor. Sponsor means the company, institution, individual donor, or organization responsible for the initiation, management or financing of a research study.

Sponsored research. Sponsored research means research funded by external entities (public, industry, or private) through a grant or contract that involves a specified statement of work (e.g., the research proposal), including clinical trials involving investigational drugs, devices or biologics.

2.2 Responsibility

Sponsor grants, contracts, and other written agreements will be reviewed for the following by the Office of Sponsored Research and/or the Office of Industry Contracting, including consultation with the IRB, as necessary:

1. All sponsor contracts have a written agreement with the Sponsor that addresses medical care for research participants with a research-related injury, when appropriate including who will provide care and who is responsible to pay for it.

2. In studies where Sponsors conduct research site monitoring visits or conduct monitoring activities remotely, the sponsor contracts have a written agreement with the Sponsor that the Sponsor promptly (no longer than within 30 days) reports to the UNC-Chapel Hill findings that could affect the safety of participants, influence the conduct of the study, or alter the IRB’s approval to continue the study.
3. When the Sponsor has the responsibility to conduct data and safety monitoring, the sponsor contracts have a written agreement with the Sponsor that addresses provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to the UNC-Chapel Hill. Contracts or other funding agreements specify the time frame for providing routine and urgent data and safety monitoring reports to the organization as indicated in the data and safety monitoring plan approved by the IRB. Investigators or the organization conducting the research are required to forward this information to the IRB.

4. Sponsor contracts have a written agreement with the Sponsor about plans for disseminating findings from the research and the roles that investigators and Sponsors will play in the publication or disclosure of results.

5. When participant safety could be directly affected by study results after the study has ended, the sponsor contracts have a written agreement with the Sponsor that the investigator or the UNC-Chapel Hill will be notified of the results in order to consider informing participants. Contracts or other funding agreements specify a timeframe after closure of the study during which the sponsor will communicate such findings (e.g., two years). This should be based on the appropriate timeframe for each individual study.

6. Payment in exchange for referrals of prospective participants from investigators (physicians) (“finder’s fees”) is not permitted. Similarly payments designed to accelerate recruitment that are tied to the rate or timing of enrollment (“bonus payments”) are also not permitted.
1 Purpose

The University of North Carolina at Chapel Hill (UNC-Chapel Hill) is committed to ensuring that educational opportunities are offered to research participants, prospective research participants, and community members which will enhance their understanding of research involving human participants at the UNC-Chapel Hill and provide them the opportunity to provide input and express concerns.

The following procedures describe how the UNC-Chapel Hill fulfills that responsibility.

2 Procedure

2.1 Responsibility

It is the responsibility of the North Carolina Translational and Clinical Sciences (NC TraCS) Institute at UNC-CH to implement the procedures outlined below.

2.2 Outreach Resources and Educational Materials

1. The OHRE dedicates a section of the website to research participants entitled “Join the Conquest”. This website includes resources, such as Frequently Asked Questions (FAQs), and a listing of relevant research-related links.

2. The site includes a “Contact Us” link that allows members of the community to ask questions, express concerns, or provide feedback. Provision of contact information by the person is optional.

3. The UNC-Chapel Hill periodically provides presentations related to research to community organizations.

4. The UNC-Chapel Hill holds an annual “Research Day” to which members of the public are invited.

2.3 Evaluation

On an annual basis, the UNC-Chapel Hill evaluates its outreach activities and makes changes when appropriate. In order to formally evaluate its outreach activities, the OHRE Director will review:
1. The specific community outreach activities being used

2. Whether or not these community outreach activities have an evaluative component (e.g., evaluation instrument distributed to participants), and if so whether the feedback was positive, negative, or neutral and if any suggestions were made that could be used to enhance future activities.

3. The number of times the “Join the Conquest” site is visited

4. Feedback provided via the “Contact Us” mechanism on the “Join the Conquest”

5. Feedback provided from other sources (unaffiliated IRB members, investigators, research staff, students, etc.)

The results of the review will be used to establish both the adequacy of current outreach activities and any additional resources that may be needed to meet the needs of the research community regarding participant outreach.
1  Purpose

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) required the creation of a Privacy Rule for identifiable health information. While the primary impact of the Privacy Rule is on the routine provision of and billing for health care, the Rule also affects the conduct and oversight of research.

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

Except as otherwise permitted, the Privacy Rule requires that a research subject “authorize” the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject’s consent to participate in research, which is required under the Common Rule and FDA regulations.

Under the Privacy Rule, a HIPAA Authorization may be combined with the consent document for research. When the consent document is combined with an Authorization, 45 CFR part 46 and 21 CFR part 56 require IRB review of the combined document.

At the UNC-Chapel Hill for exempt projects and other categories of research not subject to IRB or Privacy Board oversight, the IRB Office is designated to act upon requests for waivers and alterations of the Authorization requirement for research purposes.

2  Procedure

2.1  The IRB’s Role under the Privacy Rule

Under the Privacy Rule, IRBs gained authority to consider, and act upon, requests for a partial or complete waiver or alteration of the Privacy Rule’s Authorization requirement for uses and disclosures of PHI for research. Although DHHS and FDA Protection of Human Subjects Regulations include protections to help ensure the privacy of subjects and the confidentiality of information, the Privacy Rule supplements these protections by requiring covered entities to implement specific measures to safeguard the privacy of PHI. If certain conditions are met, an IRB may grant a waiver or an alteration of the Authorization requirement for research uses or disclosures of PHI.
The UNC-Chapel Hill has designated the UNC-Chapel Hill IRB to fulfill the functions of a Privacy Board for human subject research. The Privacy Rule does not change the composition of an IRB. The Privacy Rule permits a covered entity to accept documentation of waiver or alteration approval from any qualified IRB or Privacy Board -- not only the IRB overseeing the organization's research.

When acting upon a request to waive or alter the Authorization requirement, an IRB must follow the procedural requirements of the DHHS Protection of Human Subjects regulations and, if applicable, FDA regulations, including using either the normal review procedures (review by the convened IRB) or the expedited review procedures.

When a request for a waiver or an alteration of the Authorization requirement is considered by the convened IRB, a majority of the IRB members must be present at the meeting, including at least one member whose primary concerns are in nonscientific areas.

In order for an approval of a waiver or an alteration of the Privacy Rule's Authorization requirement to be effective, it must be approved by a majority of the IRB members present at the convened meeting. If a member of the IRB has a conflicting interest with respect to the PHI use and disclosure for which a waiver or an alteration approval is being sought, that member may not participate in the review.

DHHS and FDA have established categories of research that may be reviewed by an IRB through an expedited review procedure. Expedited review of a request for a waiver or an alteration of the Authorization requirement is permitted where the research activity is on the DHHS or FDA list of approved categories and involves no more than minimal risks. In addition, 45 CFR 46.110 and 21 CFR 56.110 permit an IRB to use an expedited review procedure to review minor changes in previously approved research.

A modification to a previously approved research plan, which only involves the addition of an Authorization for the use or disclosure of PHI to the IRB-approved informed consent, may be reviewed by the IRB through an expedited review procedure, because this type of modification may be considered to be no more than a minor change to research.

If expedited review procedures are appropriate for acting on the request, the review may be carried out by the IRB Chair or by one or more experienced reviewers designated by the Chair from among the IRB members.

A member with a conflicting interest may not participate in an expedited review. If an IRB uses expedited review procedures, it must adopt methods for keeping all its members advised of requests for waivers or alterations of the Authorization requirement as well as those requests that have been granted under an expedited review procedure.

IRB documentation of approval of a waiver or alteration of the authorization requirement includes:

- The identity of the approving IRB
- The date on which the waiver or alteration was approved
• A statement that the IRB has determined that all the specified criteria for a waiver or an alteration were met
• A brief description of the PHI for which use or access has been determined by the IRB to be necessary in connection with the specific research activity
• A statement that the waiver or alteration was reviewed and approved under either normal or expedited review procedures
• The UNC-Chapel Hill will not release PHI to investigators without individual authorization or proper documentation of an IRB or Privacy Board approval of a waiver or alteration of the requirement.

2.2 Authorization

Except as otherwise permitted, the Privacy Rule requires that a research subject “authorize” the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject’s consent to participate in research, which is required under the Common Rule and FDA regulations. Just as a valid consent under Common Rule and FDA regulations must meet certain requirements, a valid authorization must contain certain statements and core elements [45 CFR 164.508(c)]. At the UNC-Chapel Hill authorization language is generally not to be incorporated into the consent document. Template HIPAA authorization documents, which include required HIPAA authorization language, are available from the IRB. Once executed, a signed copy must be provided to the individual providing authorization. Signed authorizations must be retained by the covered entity for 6 years from the date of creation or the date it was last in effect, whichever is later.

A research subject has the right to revoke their authorization at any time. Investigators are not required to retrieve information that was disclosed under the authorization before learning of the revocation. Additionally, investigators may continue to use and disclosure PHI already obtained for the research under an authorization to the extent necessary to protect the integrity of the research.

When an Authorization permits disclosure of PHI to a person or organization that is not a covered entity (such as a sponsor or funding source), the Privacy Rule does not continue to protect the PHI disclosed to such entity. However, other federal and state laws and agreements between the covered entity and recipient such as a Business Associate Agreement (BAA) or Confidentiality Agreement may establish continuing protections for the disclosed information. Under the DHHS Protection of Human Subjects regulations or the FDA Protection of Human Subjects regulations, an IRB may impose further restrictions on the use or disclosure of research information to protect subjects.

2.2.1 Authorization Core Elements:

1. A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner.
2. The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure.

3. The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure.

4. A description of each purpose of the requested use or disclosure.

5. Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure ("end of the research study" or "none" are permissible for research, including for the creation and maintenance of a research database or repository).

6. Signature of the individual and date. If the individual’s legally authorized representative signs the Authorization, a description of the representative’s authority to act for the individual must also be provided.

2.2.2 Authorization Required Statements:

1. A statement of the individual’s right to revoke his/her Authorization and how to do so, and, if applicable, the exceptions to the right to revoke his/her Authorization or reference to the corresponding section of the covered entity’s notice of privacy practices.

2. Whether treatment, payment, enrollment, or eligibility of benefits can be conditioned on Authorization, including research-related treatment and consequences of refusing to sign the Authorization, if applicable.

3. A statement of the potential risk that PHI will be re-disclosed by the recipient. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.

2.2.3 Division of Responsibilities When one IRB Cedes Overview to Another

In the case of a separate HIPAA authorization form, the Relying Institution shall be responsible for ensuring that the form complies with applicable requirements in the HIPAA Privacy Rule. In the case of a combined consent and HIPAA authorization, the Reviewing Institution/IRB shall be responsible for ensuring that the form complies with applicable requirements in the HIPAA Privacy Rule.

2.3 Waiver or Alteration of the Authorization Requirement

Obtaining signed authorization to access and use PHI for research is not always feasible. The Privacy Rule contains criteria for waiver or alterations of authorization. If a covered entity has used or disclosed PHI for research pursuant to a waiver or alteration of authorization, documentation of the approval of the waiver or authorization must be retained for 6 years from the date of its creation or the date it was last in effect, whichever is later.

For research uses and disclosures of PHI, an IRB or Privacy Board may approve a waiver or an alteration of the authorization requirement in whole or in part. A complete waiver occurs when the IRB or Privacy Board determines that no authorization will be required for a covered entity.
to use and disclose PHI for a particular research project. A partial waiver of authorization occurs when the IRB or Privacy Board determines that a covered entity does not need authorization for all PHI uses and disclosures for research purposes, such as accessing PHI for research recruitment purposes. An IRB or Privacy Board may also approve a request that removes some PHI, but not all, or alters the requirements for an authorization (an alteration).

In order for an IRB or Privacy Board to waive or alter authorization, the Privacy Rule (45 CFR 164.512(i)(2)(ii)) requires the IRB or Privacy Board to determine the following:

1. The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
   a. An adequate plan to protect health information identifiers from improper use and disclosure.
   b. An adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a healthcare or research justification for retaining them or a legal requirement to do so).
   c. Adequate written assurances that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

2. The research could not practicably be conducted without the waiver or alteration.

3. The research could not practicably be conducted without access to and use of the PHI.

The Privacy Rule allows institutions to rely on a waiver or an alteration of Authorization obtained from a single Privacy Board to be used to obtain or release PHI in connection with a multi-site project. However, DHHS also recognizes that “covered entities may elect to require duplicate Privacy Board reviews before disclosing [PHI] to requesting researchers” (67 Federal Register 53232, August 14, 2002). 23.5

2.4 Activities Preparatory to Research

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

The covered entity must obtain from an investigator representations that (1) the use or disclosure is requested solely to review PHI as necessary to prepare a research plan or for similar purposes preparatory to research, (2) the PHI will not be removed from the covered entity in the course of review, and (3) the PHI for which use or access is requested is necessary for the research.
At the UNC-Chapel Hill, this is accomplished by the investigator submitting a Preparatory to Research request

2.5  Research Using Decedent's Information

The HRPP Office obtains from the investigator:

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

2.6  Future Uses: Databases and Repositories

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

Individual authorization for the storage of PHI for future research must be sought unless the IRB has determined that the criteria for a waiver of the authorization requirement are satisfied. See Section 23.4 of this policy manual for a discussion of waivers of authorization.

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

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

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

As with any other research, subject participation in corollary or sub-studies not essential to the primary aims of the research should be on a voluntary basis. This is particularly important when the primary research offers a potential benefit, such as treatment, that might compel the potential subject to agree to something that they otherwise would not.

HIPAA reinforces this ethical principle by explicitly stating that authorization for “unconditioned” activities, for which there is no associated treatment, benefit or other effect on the individual subject associated with participation, cannot be required. The published preamble to HIPAA Omnibus clarifies the basis for this position, and the requirement that authorization for unconditioned activities involve a clear opt-in mechanism, stating:

“This limitation on certain compound authorizations was intended to help ensure that individuals understand that they may decline the activity described in the unconditioned authorization yet still receive treatment or other benefits or services by agreeing to the conditioned authorization.” and “an opt out option does not provide individuals with a clear ability to authorize the optional research activity, and may be viewed as coercive by individuals.”

As with authorization for future research, it is acceptable to combine in a single document the authorization for a conditioned activity, such as a clinical trial, with authorization for an unconditioned activity such as a corollary or sub-study that does not directly benefit or effect the individual participant, provided that:

1. The authorization clearly differentiates between the conditioned and unconditioned research activities;
2. The authorization clearly allows the individual the option to opt in to the unconditioned research activities; and
3. Sufficient information is provided for the individual to be able to make an informed choice about both the conditioned and unconditioned activities.

Separate authorization must be obtained for each research activity that involves the use and disclosure of psychotherapy notes. For example, authorization for the use and disclosure of psychotherapy notes for a clinical trial cannot be combined with an authorization for the use and disclosure of those psychotherapy notes for a corollary research activity.

2.8 De-identification of PHI under the Privacy Rule

Covered entities may use or disclose health information that is de-identified without restriction under the Privacy Rule. The “Safe Harbor” method permits a covered entity to de-identify data by removing all 18 data elements that could be used to identify the individual or the individual’s relatives, employers, or household members. The covered entity also must have no actual knowledge that the remaining information could be used alone or in combination with other information to identify individuals. Under this method, the identifiers that must be removed are the following:
1) Names.

2) All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:

a. The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people.

b. The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.

3) All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.

4) Telephone numbers.

5) Facsimile numbers.

6) Electronic mail addresses.

7) Social security numbers.

8) Medical record numbers.

9) Health plan beneficiary numbers.

10) Account numbers.

11) Certificate/license numbers.

12) Vehicle identifiers and serial numbers, including license plate numbers.

13) Device identifiers and serial numbers.

14) Web universal resource locators (URLs).

15) Internet Protocol (IP) address numbers.

16) Biometric identifiers, including fingerprints and voiceprints.

17) Full-face photographic images and any comparable images.

18) Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.

Alternatively, a qualified statistician may certify that the risk is very small that health information could be used, alone or in combination with other available information, to identify individuals. The qualified statistician must document the methods and results of the analysis that justify such a determination. This analysis must be retained by the covered entity for 6 years from the date of its creation or when it was last acted on, whichever is later.

The Privacy Rule permits a covered entity to assign to, and retain with, the de-identified health information, a code or other means of record re-identification if that code is not derived from
or related to the information about the individual and is not otherwise capable of being translated to identify the individual. The covered entity may not use or disclose the code or other means of record identification for any other purpose and may not disclose its method of re-identifying the information.

NOTE: Data that is considered de-identified under HIPAA may still be considered human subject data under the Common Rule, particularly when working with a small data set that can be further divided into smaller subsets. Additionally, while coded information may be de-identified under HIPAA, if the investigator holds or has the ability to access both the code and the data, the information is considered identifiable private information under the Common Rule.

2.9 Limited Data Sets and Data Use Agreements

Limited data sets are data sets stripped of certain direct identifiers. Limited data sets may be used or disclosed only for public health, research, or health care operations purposes. Because limited data sets may contain identifiable information, they are still PHI and as such are not considered de-identified under the Privacy Rule. Unlike de-identified data, protected health information in limited data sets may include: addresses other than street name or street address or post office boxes, all elements of dates (such as admission and discharge dates) and unique codes or identifiers not listed as direct identifiers. The following direct identifiers must be removed for PHI to qualify as a limited data set:

1) Names;
2) postal address information, other than town or city, state, and ZIP code;
3) telephone numbers;
4) fax numbers;
5) email addresses;
6) social security numbers;
7) medical record numbers;
8) health plan beneficiary numbers;
9) account numbers;
10) certificate or license numbers;
11) vehicle identifiers and license plate numbers;
12) device identifiers and serial numbers;
13) URLs;
14) IP addresses;
15) biometric identifiers; and
16) full-face photographs and any comparable images.
Before disclosing a limited data set, a covered entity must enter into a data use agreement (DUA) with the recipient, even when the recipient is a member of its workforce. The data use agreement establishes the parameters around the proposed uses and disclosures of the data, who is permitted to have access to the data, and stipulates that no other use will be made of the data, no attempt will be made to identify or contact individuals whose data are included in the limited data set, that appropriate safeguards are in place to protect the data from unauthorized use and that the recipient will report any uses or disclosures of the PHI that they become aware of that not in keeping with the terms of the DUA. Data Use Agreements for the purposes of research are available through the ice of Industry Contracting. Data Use Agreements should be submitted to the IRB along with the other project materials so that the UNC-Chapel Hill IRB has a record of the agreement.

2.10 Research Subject Access to PHI

With few exceptions, the Privacy Rule guarantees individuals access to their medical records and other types of health information. One exception is during a clinical trial, when the subject’s right of access can be suspended while the research is in progress. The subject must have been notified of and agreed to the temporary denial of access when providing consent and authorization. Any such notice must also inform the individual that the right to access will be restored upon conclusion of the clinical trial. Language accommodating this exclusion is included in the applicable the UNC-Chapel Hill research consent/authorization templates.

2.11 Accounting of Disclosures

The Privacy Rule generally grants individuals the right to a written “Accounting of Disclosures” of their Protected Health Information made by a covered entity without the individual’s authorization in the six years prior to their request for an Accounting. A covered entity must therefore keep records of such PHI disclosures for 6 years.

It is important to understand the difference between a use and a disclosure of PHI. In general, the use of PHI means communicating that information within the covered entity. A disclosure of PHI means communicating that information to a person or entity outside the covered entity. The Privacy Rule restricts both uses and disclosures of PHI, but it requires an accounting only for certain PHI disclosures.

Generally, an Accounting of Disclosures is required for:

1) Routinely Permitted Disclosures (e.g., under public health authority, to regulatory agencies, to persons with FDA-related responsibilities) with limited exceptions (e.g., law enforcement, national security, etc.)

2) Disclosures made pursuant to:
   a. Waiver of Authorization
   b. Research on Decedents’ Information
   c. Reviews Preparatory to Research
An accounting is not needed when the PHI disclosure is made:

1) For treatment, payment, or health care operations.
2) Under an Authorization for the disclosure.
3) To an individual about himself or herself.
4) As part of a limited data set under a data use agreement.

The Privacy Rule allows three methods for accounting for research-related disclosures that are made without the individual's Authorization or other than a limited data set: (1) A standard approach, (2) a multiple-disclosures approach, and (3) an alternative for disclosures involving 50 or more individuals. Whatever approach is selected, the accounting is made in writing and provided to the requesting individual. Accounting reports to individuals may include results from more than one accounting method.

See the UNC-Chapel Hill Accounting of Disclosures of Protected Health Information (PHI) Policy for a detailed discussion on Accounting for Disclosures.

3 Definitions

**Access.** Access is the mechanism of obtaining or using information electronically, on paper, or other medium for the purpose of performing an official function.

**Accounting of Disclosures.** Information that describes a covered entity's disclosures of PHI other than for treatment, payment, and health care operations; disclosures made with Authorization; and certain other limited disclosures. For those categories of disclosures that need to be in the accounting, the accounting must include disclosures that have occurred during the 6 years (or a shorter time period at the request of the individual) prior to the date of the request for an accounting. However, PHI disclosures made before the compliance date for a covered entity are not part of the accounting requirement.

**Authorization.** An individual's written permission to allow a covered entity to use or disclose specified PHI for a particular purpose. Except as otherwise permitted by the Privacy Rule, a covered entity may not use or disclose PHI for research purposes without a valid Authorization.

**Covered entity.** A health plan, a health care clearinghouse, or a health care provider who transmits health information in electronic form in connection with a transaction for which DHHS has adopted a standard.

**Data Use Agreement.** An agreement into which the covered entity enters with the intended recipient of a limited data set that establishes the ways in which the information in the limited data set may be used and how it will be protected.

**Designated Record Set.** A group of records maintained by or for a covered entity that includes (1) medical and billing records about individuals maintained by or for a covered health care provider; (2) enrollment, payment, claims adjudication, and case or medical management record systems maintained by or for a health plan; or (3) used, in whole or in part, by or for the
covered entity to make decisions about individuals. A record is any item, collection, or grouping of information that includes PHI and is maintained, collected, used, or disseminated by or for a covered entity.

**Disclosure.** The release, transfer, access to, or divulging of information in any other manner outside the entity holding the information.

**Health Information.** Health Information means any information, whether oral or recorded in any form or medium, that (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.

**Individually Identifiable Health Information.** Information that is a subset of health information, including demographic information collected from an individual, and (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; and (a) that identifies the individual; or (b) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

**Limited Data Set.** Refers to PHI that excludes 16 categories of direct identifiers and may be used or disclosed, for purposes of research, public health, or health care operations, without obtaining either an individual’s Authorization or a waiver or an alteration of Authorization for its use and disclosure, with a data use agreement.

**Minimum Necessary.** The standard that uses the least information reasonably necessary to accomplish the intended purpose of the use, disclosure, or request. Unless an exception applies, this standard applies to a covered entity when using or disclosing PHI or when requesting PHI from another covered entity. A covered entity that is using or disclosing PHI for research without Authorization must make reasonable efforts to limit PHI to the minimum necessary. A covered entity may rely, if reasonable under the circumstances, on documentation of IRB or Privacy Board approval or other appropriate representations and documentation under section 164.512(i) as establishing that the request for protected health information for the research meets the minimum necessary requirements.

**Privacy Board.** A board that is established to review and approve requests for waivers or alterations of Authorization in connection with a use or disclosure of PHI as an alternative to obtaining such waivers or alterations from an IRB. A Privacy Board consists of members with varying backgrounds and appropriate professional competencies as necessary to review the effect of the research plan on an individual’s privacy rights and related interests. The board must include at least one member who is not affiliated with the covered entity, is not affiliated with any entity conducting or sponsoring the research, and is not related to any person who is affiliated with any such entities. A Privacy Board cannot have any member participating in a review of any project in which the member has a conflict of interest.
Protected Health Information. PHI 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 individually identifiable health information in 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.

Use. With respect to individually identifiable health information, the sharing, employment, application, utilization, examination, or analysis of such information within the entity or health care component (for hybrid entities) that maintains such information.

Waiver or Alteration of Authorization. The documentation that the covered entity obtains from an investigator or an IRB or a Privacy Board that states that the IRB or Privacy Board has waived or altered the Privacy Rule’s requirement that an individual must authorize a covered entity to use or disclose the individual’s PHI for research purposes.

Workforce. Employees, volunteers, trainees, and other persons whose conduct, in the performance of work for a covered entity, is under the direct control of the covered entity, whether or not they are paid by the covered entity.
1 Purpose

The University of North Carolina at Chapel Hill (UNC-Chapel Hill) has established standards and safeguards to protect patient’s information and to ensure compliance with federal and state information security regulations.

2 Procedure

It is the responsibility of investigators to familiarize themselves with and comply with these standards. The use of personal laptops, desktops, portable/USB drives, and other non-UNC-Chapel Hill devices for storage of research data is discouraged. In the instances when a non UNC-Chapel Hill computer or device must be used for the purposes of storing, even temporarily, or transmitting PHI or PII (Personally Identifiable Information) for research, the safeguards of the device must be verified by the person within the department who is responsible for data security. Additionally, all potential or known breaches of research data must be immediately reported to the IRB so that appropriate steps can be taken to assess the situation, protect the information, and comply with regulations. Lost or stolen the UNC-Chapel Hill devices containing research data must also be reported to the IRB.

Provisions for Data Security must be described in applications to the IRB and updated as necessary. When information containing direct identifiers such as Social Security numbers or PHI including data considered sensitive is to be transferred outside of the institution, the provisions for data security may be subject to further review and approval by the School IT Directors (also the Information Security Liaison) in consult with ITS Security.

In the event of a security breach, as defined by the University’s “Data Security Breach Protocol,” (http://policies.unc.edu/policies/breach-protocol/) the matter must be reported immediately to the Information Technology Resources Center at 919-962-HELP or Campus Police at 919-962-8100, as specified in the Protocol.

See the UNC-Chapel Hill Policies on Patient Privacy and Information Security for further information: http://its.unc.edu/about-us/how-we-operate/
1 Research supported by the Department of Defense (DoD)

Research supported by the Department of Defense (DoD) is reviewed and conducted in compliance with part 219 of title 32 CFR, part 980 of title 10 USC, applicable parts of title 21 CFR (50, 56, 312, 600, 812), DoD Instruction 3216.02, DoD Directive 3210.07, and applicable additional requirements from respective DoD component(s).

1.1 Application and Scope

The following additional requirements apply to all biomedical and social/behavioral research involving human research participants conducted under the jurisdiction of UNC-Chapel Hill when it:

- Conducts, reviews, approves, oversees, supports manages otherwise is contractually subject to regulation by the DoD; and/or
- Human subject research performed under the jurisdiction of UNC-Chapel Hill using DoD property, facilities, or assets.

In most cases, protocols covered by these requirements also will have review, approval and oversight by the DoD Human Research Protections Program.

UNC-Chapel Hill assures that DoD supported research complies with all relevant DoD human subjects protection requirements, including but not limited to:

- The Belmont Report
- Title 21 Code of Federal Regulations 50, 56, 312, and 812, Food and Drug Administration (FDA) Regulations
- DoDD 3216.02, “Protection of Human Subjects and Adherence to Ethical Standards in DoD-supported Research”
- Title 10 United States Code Section 980 (10 USC 980), “Limitation on Use of Humans as Experimental Subjects”
- DoDD 3210.7, “Research Integrity and Misconduct”
1.2 Key Additional Requirements Not Covered by Title 45 CFR 46, Subparts B, C and D; 21 CFR 50, 56, 312, and 812

1. **Minimal Risk – [DoDI 316.02, enclosure 3, para 6b]**

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

2. **Undue Influence – [DoDD 3216.2, enclosure 3, para 7e1]**

   Service members shall follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty and for approving off-duty employment or activities. Superiors (e.g., military and civilian supervisors, unit officers, and noncommissioned officers (NCOs)) are prohibited from influencing the decisions of their subordinates (e.g., junior enlisted personnel and equivalent civilians) regarding participation as subjects in research involving human subjects. Unit officers and senior NCOs in the chain of command shall not be present at the time of research subject solicitation and consent during any research recruitment sessions in which members of units under their command are afforded the opportunity to participate as research subjects. When applicable, officers and NCOs so excluded shall be afforded the opportunity to participate as research subjects in a separate recruitment session. During recruitment briefings to a unit where a percentage of the unit is being recruited to participate as a group, an ombudsman not connected in any way with the proposed research or the unit shall be present to monitor that the voluntary nature of individual participants is adequately stressed and that the information provided about the research is adequate and accurate.

3. **Education and Training – [DoDD 3216.2, enclosure 3, para 5]**

   For initial and continuing research ethics education for all personnel who conduct, review, approve, oversee, support, or manage human participant research, there may be specific DoD educational requirements or certification required. The IRB shall use this guidance document as the basis for reviewing any DoD supported research and shall ensure that the PI has received this document before approving the research. The DoD component may evaluate the education policies to ensure the personnel are qualified to perform the research, based on the complexity and risk of the research.

4. **Appointment of a Research Monitor – [DoDI 3216.02, enclosure 3, para 8]**
• The IRB considers the appointment of a research monitor:
  o Required for research involving greater than minimal risk, although the IRB or
    organizational official can require this for a portion of the research or studies
    involving no more than minimal risk if appropriate.
  o The research monitor is appointed by name and shall be independent of the
    team conducting the research.
  o There may be more than one research monitor (e.g. if different skills or
    experience are needed.
  o The monitor 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.
  o The IRB or HRPP official shall communication with research monitors to confirm
    their duties, authorities, and responsibilities.
  o The duties of the research monitor are determined on the basis of specific risks
    or concerns about the research.
    ▪ 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.
• The research monitor has the authority to:
  ▪ Stop a research study in progress.
  ▪ Remove individuals from study.
  ▪ Take any steps to protect the safety and well-being of participants until
    the IRB can assess.

5. Additional protections for pregnant women, prisoners, and children (Subparts B, C and D)
   of 45 CFR 46) – [DoDi 3216.02, enclosure 3 para 7]

• Research involving pregnant women, prisoners, and children are subject to the DHHS
  Subparts B, C. and D.
  o For purposes of applying Subpart B, the phrase “biomedical knowledge” shall
    be replaced with “generalizable knowledge.”
  o 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.
  o Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter
    III, Part H, 289g.
  o 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.
  o Research involving a detainee as a human participants is prohibited. This prohibition does not apply to research involving investigational drugs and devises when the same products would be offered to US military personnel in the same location for the same condition.
• Research involving prisoners cannot be reviewed by the expedited procedure.
• When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum.
• In addition to allowable categories of research on prisoners in Subpart C, epidemiological research is also allowable when:
  o The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.
  o The research presents no more than minimal risk
  o The research presents no more than an inconvenience to the participant.
• When a prisoner becomes a participant, 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 organizational 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 re-review the research protocol to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert having the expertise of a prisoner representative if the IRB reviewing the research protocol does not have a prisoner representative. If the prisoner-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 recruitment of prisoners as participants.

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

If the research participant meets the definition of “experimental subject,” policies and procedure 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 necessarily 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.

Research involving a human being as an experimental subject is an activity, for research purposes, where there is an intervention or interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction. If the research participant does not meet the definition of “experimental subject,” policies and procedure allow the IRB to waive the consent process.

For classified research, waivers of consent are prohibited.


The Dual Compensation Act prohibits an individual from receiving pay from more than one position for more than an aggregate of 40 hours of work in one calendar week. This prohibition applies to employees paid from either appropriated or non-appropriated funds, or a combination thereof, and includes temporary, part-time and intermittent appointments. This law is not applicable to enlisted off-duty military personnel in relation to their military duty.

When research involves U.S. military personnel, limitations on dual compensation include:

- 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.
- 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.

8. **Requirement for Reporting - DoDI 3216.02, enclosure 3 para 4(b)(4)**

The Institution shall promptly (no longer than within 30 days) notify the HRPO of the following: when significant changes to the research protocol are approved by the IRB, the results of the IRB continuing review, if the IRB used to review and approve the research changes to a different IRB, when the institution is notified by any Federal department or agency or national organization that any part of its HRPP is under investigation for cause involving a DoD-
supported research protocol, and all UPIRTSOs, suspensions, terminations, and serious or continuing noncompliance regarding DoD-supported research involving human subjects.

9. **Recordkeeping Requirements** - [DoDD 3216.2, para. 5.3.2; SECNAVINST 3900.39D, para. 8c(18)]

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

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

10. **Addressing and Reporting Allegations of Non-Compliance with Human Research Protections** - [DoDD 3216.2, para. 4.10; SECNAVINST 3900.39D, para. 8d(2) and 6k]

Report the initiation of all investigations and report results regardless of the findings to the Navy Secretary General and appropriate sponsors.

11. **Addressing and Reporting Allegations of Research Misconduct** - [DoDD 3216.2, para. 4.8; DODD 3210.7; SECNAVINST 3900.39D, para. 6d(2) para. 6l]

All findings of serious research misconduct under this section shall be reported to the Director, Defense Research and Engineering.

12. **Provisions for Research with Human Subjects using Investigational Test Articles (Drugs, Device and Biologics)** - [DoDD 3216.2, para 4.9; DoDD 6200.2; SECNAVINST 3900.39D, para. 6h]

Principal investigators may not be sponsors for INDs and IDEs.

13. **Prohibition of Research with Prisoners of War (POW) and Detainees** - [DoDD 3216.2, para 4.4.2; SECNAVINST 3900.39D, para. 6a(8)]

Research involving any person captured, detained, held or otherwise under the control of DoD personnel (military and civilian, or contractor employee) is prohibited.

14. **Classified research** [DoDI 3216.02, enclosure 3 para 13]

The involvement of classified information may be limited to information needed for IRB approval and oversight of the research; information needed to inform the human subjects during the consent process; and information provided by the human subjects during the course of the research. Secretary of Defense approval is required for all classified non-exempt research involving human subjects.
Informed consent procedures shall include:
(1) Identification of the Department of Defense as the supporting institution of the research, unless the research involves no more than minimal risk. The Secretary of Defense may grant an exception to this requirement on the grounds that providing this information could compromise intelligence sources or methods.
(2) A statement that the research involving human subjects is classified and an explanation of the impact of the classification.

The IRB shall determine whether potential human subjects need access to classified information to make a valid, informed consent decision.

IRB review shall be conducted using a full board review. Use of an expedited review procedure is prohibited.

15. Additional Requirements for DoD Sponsored Research

a) New research and substantive scientific amendments to approved research shall undergo scientific review and the review is considered by the IRB. The IRB may rely on outside experts to provide an evaluation of scientific merit.

b) When conducting research with international populations, additional safeguards for research conducted with international populations include: The Organization or Researcher has permission to conduct research in that country by certification or local ethics review and the Researcher follows all local laws, regulations, customs, and practices.

c) Disclosure regarding the provisions for research-related injury follow the requirements of the DoD component.

d) 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.

e) When conducting multi-site research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.

f) The following shall be promptly (no longer than within 30 days) reported to the DoD human research protection officer:
   a. When significant changes to the research protocol are approved by the IRB.
   b. The results of the IRB continuing review.
   c. Change of reviewing IRB.
   d. When the organization is notified by any Federal department, agency or national organization that any part of the HRPP is under investigation for cause involving a DoD-supported research protocol.

g) If consent is to be obtained from the research participant’s LAR, the research must intend to benefit the individual participant. The determination that research is intended to be beneficial to the individual research participant must be made by the IRB.
1.3 Responsibilities

It is the responsibility of the principal investigator to ensure compliance with all additional Department of Defense (DoD) requirements for human subject protection. It also is the responsibility of the IRB to ensure that all additional requirements by Department of Defense components for human subject protection have been met before IRB approval of the research project.

1.4 DoD Definitions

**Research Involving Human Subjects:** An activity that includes both a systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information, or activities covered by section 32 CFR 219.101 (including exempt research involving human subjects) and DoD Instruction 3216.02.

**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.
1 Purpose

Consistent with the University of North Carolina at Chapel Hill’s research, teaching and public service missions, the University encourages faculty, staff and students to engage in appropriate outside relationships, including but not limited to private industry and the nonprofit sector. Members of the University community are expected to avoid conflicts of interest that have the potential to directly and significantly affect the University’s interests; compromise objectivity in carrying out University responsibilities; or otherwise compromise performance of University responsibilities, unless such conflicts are disclosed, reviewed, and managed in accordance with the Policy on Individual Conflicts of Interest and Commitment.

It is the University of North Carolina at Chapel Hill’s (UNC-CH) policy on Individual Conflicts of Interest and Commitment to preserve public trust in the integrity and quality of research through the management, reduction or elimination of actual, potential or perceived conflicts of interest in the conduct of research.

2 Researcher Conflicts of Interest

Conflicts of interest (COI) in research can be broadly described as any interest that competes with the integrity of a research study, or the credibility of the research program or an individual’s obligation to protect the rights and welfare of research subjects. At the University, conflicts of interest can be financial or non-financial; any type must be disclosed as applicable. In general, a “financial Interest related to the research” means a financial interest in the sponsor, product or service being tested but it can extend beyond this definition based on the context of the study.

Some of the general standards the University maintains regarding conflict of interest (COI) and research are:

- All individuals who engage in research are required to take and maintain COI training.
- Any individual in a role will be requiring COI disclosure will need to disclose, at minimum, their own activities, interests and relationships as well as those of a spouse/partner and dependent child(ren).
- A zero dollar threshold of disclosure is required so that even uncompensated relationships may need to be disclosed.
- Similar to any involvement in human studies research, there is a higher standard for conflict of interest review and possible management related to a human study.

For more detailed information, please consult the Policy on Individual Conflicts of Interest and Commitment as well as the associated Standard Operating Procedures on Individual Conflicts of Interest and Commitment.
For human studies, in the event the conflict of interest cannot be effectively managed to its satisfaction, the IRB retains the authority to disapprove the research. When the financial interest is directly related to the human subjects’ research and may be substantially affected by it, the risk is greatest and the bar must be high.

3 Conflict of Interest Procedures

3.1 COI Disclosure

The IRB application requires certain key members of the study team who will be involved in the design, conduct or reporting of the human study to file Conflict of Interest (COI) disclosures. These individuals are required to disclose based on their role on the study, which are reflective of their institutional duties.

Disclosure requirements apply to any researchers and research staff who are subject to UNC-CH policies. Personnel subject to their home institution’s COI policies (e.g., EPA, other universities) are not required to submit separate disclosures through the UNC-CH COI Program. Non-UNC study personnel are required to submit documentation of compliance with their home institution’s COI policies for their work on the IRB study. Non-UNC study personnel who are not covered by a home institution’s policies are expected to comply with UNC-CH policies related to research.

3.2 University review coordination with IRB

When a principal investigator initially submits a human subjects research study to the IRB for review, the electronic system automatically creates Conflict of Interest (COI) disclosures in the Activities, Relationships and Interests system (air.unc.edu) for all applicable persons named on a human subjects research study. These persons are notified immediately by email of the requirement to complete the COI disclosure.

Upon completion of a disclosure by the applicable research personnel, the COI system programmatically evaluates that disclosure for a potential COI. If a potential COI is identified by the system, the disclosure is flagged for review and routed to the COI Program office.

All specified personnel needing COI disclosure named on a human subjects research study are required to update their disclosures at least annually in conjunction with the annual renewal, or if newly added to the human study or if there is an additional sponsor. Individuals can also self-submit a disclosure through the electronic system to indicate any change in an external activity, interest or relationship and are required to submit if there is change in an interest or relationships within thirty (30) days.

When the COI Program receives a COI disclosure disclosing a potential conflict of interest in the human studies research, the staff at COI Program conducts a preliminary review and provides appropriate information to the applicable school conflict of interest committee chair(s) in accordance with its standard process. For further details, please see Standard Operating Procedures for Individual Conflicts of Interest.

In the case of human subject research, the UNC-CH IRB is also informed automatically through the electronic system of a pending conflict undergoing review for a particular individual. In the case of complex review, an IRB Chair and/or Analyst may be invited to attend a COI Committee meeting to partake in the analysis.
The applicable University conflict of interest review chair and/or committee provides to the IRB any written determination of the conflict of interest and its resolution, including any conditions or management plans that are put in place regarding the conflict(s) for the specific human subjects research study. These details are automatically visible to the IRB through the electronic system for each human research study.

Approval of a conflict of interest and its associated management plan by a University Conflict of Interest Chair and/or Committee does not obligate an IRB to approve an individual’s involvement in a proposed human subjects research activity. The UNC Chapel Hill IRB retains the final approval and authority as to whether human subjects research may in fact proceed.

If the COI Committee has not completed its review, the IRB will not issue its approval for the research study or will prohibit participation by the researcher with a potential COI until the COI Committee review process is completed and the results are made available to the IRB for its consideration.

### 3.2 Evaluation of COI

The University’s Policy on *Conflicts of Interest and Commitment* includes a rebuttable presumption that an investigator may not conduct human subjects’ research that is related to a financial interest of the investigator (or immediate family) except in compelling circumstances.

Compelling circumstances are those facts that convince the reviewer that a covered individual who has a financial interest should be permitted to conduct human subjects’ research, taking into account the following factors:

- The nature of the research,
- The nature and magnitude of the financial interest
- How closely the financial interest is related to the research
- The extent to which the interest may be affected by the research
- The degree of risk to the human subjects involved that is inherent in the research protocol
- The extent to which the investigator is uniquely qualified to perform a research study with important public benefit
- The extent to which the interest is amenable to effective oversight and management.

The applicable COI Chair and/or Committee takes into these criteria into account when reviewing any disclosed conflict of interest in the context of the human study. The COI Chair or Committee considers the following factors into their review:

- How the research is supported or financed,
- The nature and extent of the conflict,
- The role and responsibilities of the conflicted individual in the design, conduct, and reporting of the research, and
- The ability of the conflicted individual to influence the outcome of the research.
The IRB has final authority to determine whether the research, the COI, and the related management plan, if any, allow the research to be approved.

### 3.4 Management of COI

With regard to the human study specific management determined by the applicable COI Chair or Committee, the IRB shall either accept or indicate changes to strengthen it. The IRB can require additional measures to manage a COI so that the research may be approved. However, the IRB cannot weaken a managed plan determined by a COI Chair or Committee.

Standard examples of items that can be included in a human study specific management plan from a COI Chair or Committee include:

- Disclosure of the COI to subjects through the consent process
- Modification of the research plan or safety monitoring plan
- Monitoring of research by a third party
- Disqualification of the conflicted party from participation in all or a portion of the research such as consenting, Adverse Event determination or data analysis
- Appointment of a non-conflicted PI
- Divestiture of significant financial interests or maintenance below a certain threshold in order to participate as the principal investigator
- Severance of relationships that create actual or potential conflicts

The IRB may also add any one of these standard elements to the management plan or decide upon additional restrictions to a conflicted individual’s involvement in the proposed human study research.

The IRB will review the COI and associated management plan to determine whether:

- The COI affects the rights or welfare of research subjects,
- The COI might adversely affect the integrity or credibility of the research or the research program, and
- The management plan effectively protects research subjects and the integrity and credibility of the research and the research program

The IRB will convey any additional requirements for the human subject specific management plan to the COI Program for conveyance to the applicable COI Chair and/or Committee.

Monitoring of any conflicts and adherence to a management plan is maintained by the COI Program in conjunction with the applicable COI Committee and/or Dean of the School. For further information please see Standard Operating Procedures for *Individual Conflicts of Interest*. The OHRE monitors adherence of the human subject specific plan including such items as disclosure text in the informed consent and maintenance of study specific roles. If any items arise through a monitoring process which may have implications for any human study, the COI Program notifies the OHRE of the changed circumstance so that additional review can occur, if applicable.

### 3.5 Coordination with Other IRBs

If an investigator is participating in a multi-center trial and has been allowed to conduct human subjects research while possessing a financial or personal interest, that fact should be made known to the PI or
sponsor by the coordinating center. It is the responsibility of the investigator to convey the UNC COI Finalization letter which provides the overview of the conflict and project specific management details.

Notification of research subjects falls within the purview of the applicable reviewing IRB, which will determine how the conflict of interest should be disclosed to the relevant human research subjects. This may include a description in the consent form of the conflict of interest.

References:
University of North Carolina at Chapel Hill Policy on Individual Conflicts of Interest and Commitment
University of North Carolina at Chapel Hill Standard Operating Procedures on Individual Conflicts of Interest and Commitment
45 CFR 50 Subpart F and 45 CFR 94
21 CFR 54.1, 21 CFR 54.2, 21 CFR 54.4, 21 CFR 312.64(d), 21 CFR 812.110(d)
1 Purpose

This policy outlines the responsibilities of IRB members for making known any potential or perceived conflicts of interest (COI) concerning protocols reviewed by the IRB. No IRB member may participate in the review of any research project in which they have a COI, except to provide information, as requested. It is the responsibility of each IRB member to disclose any COI related to a study submitted for review and to recuse him/herself from the deliberations and vote by leaving the room.

2 IRB Member and Consultant Conflict of Interest

IRB Members and Consultants are responsible for making known any potential or perceived conflicts of interest (COI) concerning protocols reviewed by the IRB. These conflicts could include the IRB member’s/consultant’s role in any of the following categories of activity with respect to the study in question:

- Acting as Principal Investigator, Co-Principal Investigator or other key personnel
- Personally receiving funding or funded effort from the study, as listed in the study budget
- Acting in a supervisory role over the PI of the study,
- Being involved in research utilizing a competing technology such that the ability to render an objective assessment could be compromised; or
- Being a family member involved in a close personal relationship with a member of the study team (for example, as a spouse or immediate family member)

An IRB member or consultant is considered to have a conflicting interest when the member/consultant or their immediate family has any of the following:

- Involvement in the design, conduct, or reporting of the research with the following exception:

An IRB member who is listed on an IRB protocol as a member of the study’s Key Personnel but whose study-related activities are limited to (i) the performance of commercial services for the investigator (or performing other genuinely non-collaborative services meriting neither professional recognition nor publication privileges), while (ii) adhering to commonly recognized professional standards for
maintaining privacy and confidentiality, is not considered to have a conflicting interest on this basis.

- Supervisory role over the principal investigator of the research.
- A conflict of interest management plan issued by the UNC COI Office overlapping with the research.
- Stock ownership or stock options, equity, or other financial interest related to the research valued at $5,000 or more.
- Personal compensation of $5,000 or more related to the research.
- Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright or licensing agreement.
- Board or executive relationship related to the research, such as an Advisory Board or Board of Directors, regardless of compensation.
- Any other reason for which the member or consultant believes that he or she cannot provide an independent review.

Board members and consultants should make known any conflict of interest prior to the beginning of the Board’s discussion of the protocol under review. They must leave the meeting room prior to the Board’s deliberation and vote.

Additionally, IRB members are responsible for self-identifying any conflicting interests before conducting review using the expedited procedure, so as to remove themselves from involvement in the review of the research.

The IRB members with a conflict are documented in the meeting minutes as “recused” with reason of “conflict of interest” with a notation that the member was not present for the final deliberation and vote.

3 Definitions

“Immediate Family” means spouse and dependent children.

“Financial Interest Related to the Research” means financial interest in the sponsor, product or service being tested. The definition is at least as stringent as the level of an investigator’s financial interest that requires evaluation as a possible conflict of interest.
1 Research Subject to U.S. Environmental Protection Agency Regulations

Environmental Protection Agency (EPA) policy requires that researchers submit IRB determinations and approval to the EPA human subjects research review official for final review and approval before the research can begin.

For research not conducted or supported by any federal agency that has requirements for protecting human research subjects and for which the intention of the research is submission to the EPA, the EPA requirements for protecting human research subjects apply.

Researchers must submit IRB determinations and approval to the EPA human subjects research review official for final review and approval before the research can begin.

All covered human research conducted or supported by Environmental Protection Agency (EPA) must be compliant with 40 CFR 26 and EPA Order 1000.17 Change A1. 40 CFR 26 includes EPA-specific additional protections and prohibitions for children, pregnant women and fetuses, and nursing women in research conducted or supported by the Agency at Subparts B-D. It also contains regulations for third-party human research for pesticides and rules for data use, compliance oversight, and other matters. EPA Order 1000.17 Change A1 requires that all human subjects research conducted by EPA be reviewed and approved by the EPA Human Subjects Research Review Official (HSRRO) as compliant with 40 CFR 26, or be determined to be exempt research, before the research begins. This requirement is in addition to IRB review and approval, and it occurs subsequent to it as the final step before the research commences.

- **Subpart B** of the regulations prohibits intentional exposure research, under all circumstances, in children and women who are pregnant or nursing. The ban is categorical and is not based on a risk-benefit ratio, including prospect of direct benefit.

- **Subpart C** establishes rules for studies that involve pregnant women (and thus their fetuses) participating in observational research. Research of this nature can be conducted when there is direct benefit to the woman or the fetus. However, in the absence of direct benefit, if the risk is no greater than minimal to the fetus and the research is important for biomedical knowledge which cannot be obtained in any other manner, the research is permissible.
• Subpart D establishes rules for studies that involve children participating in observational research. Research of this nature can be conducted on children as long as it involves no more than minimal risk. Research that involves greater than minimal risk can only be conducted when there is direct benefit to the subject. There is no provision in the EPA rule for the conduct of research when there is greater than minimal risk and no direct benefit to the child.

Unlike the regulations adopted by the Department of Health & Human Services, EPA's regulations:

• Do not further regulate research involving prisoners, beyond those additional protections found in the Common Rule.

• Define a child as someone less than 18 years of age (whereas HHS regulations defer to state or local law).

• Contain no exceptions to the rule prohibiting intentional exposure research involving children, nursing women, and pregnant women and fetuses

• Do not recognize a category of research on children involving "a minor increase over minimal risk."

• Have no provisions for "research not otherwise approvable" for children, nursing infants, or fetuses.

• The IRB is permitted to approve observational research involving children that does not involve greater than minimal risk only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in 26.406.

• The IRB is permitted to approve observational research involving children that involves greater than minimal risk but presenting the prospect of direct benefit to the individual subjects if the IRB finds and documents that:

  o The intervention or procedure holds out the prospect of direct benefit to the individual subject or is likely to contribute to the subject's well-being.

  o The risk is justified by the anticipated benefit to the subjects.

  o The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.

  o Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 26.406.
Research Subject to the US Department of Education Regulations

The following special considerations apply to all research involving human subjects supported or conducted by the U.S. Department of Education. These considerations are in addition to those found in 45 CFR 46 Subparts A-D.

- All instructional material—including teachers’ manuals, films, tapes, or other supplementary instructional material—which will be used in connection with any research or experimentation program or project must be available for inspection by the parents or guardians of the children engaged in such research.

- Research or experimentation program or project means any program or project in any research that is designed to explore or develop new or unproven teaching methods or techniques.

- Children are persons enrolled in research not above the elementary or secondary education level, who have not reached the age or majority as determined under state law.

1.1 Research Subject to the Family Educational Rights and Privacy Act (FERPA)

The Family Educational Rights and Privacy Act (FERPA) protects the privacy of student education records. The term “education records” includes any information that directly relates to a student and is maintained by an educational institution. In general, FERPA provides that, with certain exceptions, information from a student’s education records may not be released to others, including those within the same educational institution, without the student’s or parent’s prior written consent. If the student is over 18 or enrolled in college, the student must give the consent. If the student is under 18 and not enrolled in college, the consent must come from his or her parent. For a FERPA consent to be effective, the researcher obtain written consent from each individual whose records will be accessed for research purposes. This can be embedded in the consent form and must include the following:

- Be in writing;
- Signed and dated by the student or parent (as applicable);
- Specify the records that may be disclosed;
- State the purpose of the disclosure; and
• Identify the party to whom the records may be released.

Otherwise the Office of the University Registrar is required to approve access to student records for research purposes.

Notably, FERPA does not apply to schools that do not receive funds under a program of the U.S. Department of Education (e.g., certain private or parochial schools).

Note that health records pertaining to students, which are created and maintained by an educational institution (e.g., Campus Health Services; school nurses) are covered by FERPA rather than the Health Insurance Portability and Accountability Act (HIPAA). Accordingly, educational institutions must observe the restrictions and requirements of FERPA, including obtaining a valid FERPA consent (described above) or meeting a relevant exception (described below), before such records may be released.

In the research context, information from education records may be released, without the student’s or parent’s consent, to organizations conducting studies for, or on behalf of, educational agencies or institutions, but only if the study is:

1. for developing, validating, or administering [academic] predictive tests;
2. to administer student aid programs; or
3. to improve instruction.

In order to qualify for this exception, the study must be conducted in such a way that parents and students may not be personally identified by anyone other than those working on the study, and the identifying information must be destroyed when it is no longer needed for the study’s purposes. If the study at issue involves the University’s data, there must be a written agreement between the University and the organization (e.g., school district or post-secondary institution) conducting the study. That agreement must:

• Specify the purpose, scope and duration of the study or studies and the information to be disclosed;
• The determination of the exception;
• Require that the organization use personally identifiable information from education records only to meet the purpose or purposes of the study stated in the written agreement and must contain the current requirements in 34 CFR 99.31(a)(6) on re-disclosure and destruction of information;
• The information to be disclosed;
• Require the organization to conduct the study in such a way that there is no personal identification of parents and students by anyone other than representatives of the organization who have legitimate interests;
• Require the organization to return to the University or destroy the personally identifiable information when it is no longer needed for purposes of the study; and
• Specify the time period within which the organization must either return or destroy the personally identifiable information.

Education records may be released without consent under FERPA if all personally identifiable information has been removed including:

• Student’s name and other direct personal identifiers, such as the student’s social security number or student number.

• Indirect identifiers, such as the name of the student’s parent or other family members; the student’s or family’s address, and personal characteristics or other information that would make the student’s identity easily traceable; date and place of birth and mother’s maiden name.

• Biometric records, including one or more measurable biological or behavioral characteristics that can be used for automated recognition of an individual, including fingerprints, retina and iris patterns, voiceprints, DNA sequence, facial characteristics, and handwriting.

• Other information that, alone or in combination, is linked or linkable to a specific student that would allow a reasonable person in the school community, who does not have personal knowledge of the relevant circumstances, to identify the student with reasonable certainty.

Directory information publicly maintained by an educational institution may also be released without the student’s or parent’s consent, provided that the student or parent (as applicable) has not opted out of directory information disclosures. Researchers must check to confirm that a student has not opted out before accessing or disclosing directory information absent written consent. Researchers can verify whether a student has opted out of directory information disclosures by checking the relevant, publicly-available directory (e.g., the University’s online directory) or asking the appropriate administrative office of the educational institution (e.g., the Office of the University Registrar).

OTHERWISE, you must submit a request to the provost office as follows:

The Office of the University Registrar is required to approve access to student records for research purposes. Please submit via email a pdf copy of your IRB application to the Assistant Provost and University Registrar.

You may create a pdf copy of your IRB application by clicking on the PDF icon in the upper right corner of the Application Status screen.

After you have received approval from the Office of the University Registrar, please attach it to your IRB application.
DO NOT begin human subject interaction until the IRB has reviewed your application and made an NHSR determination, Exempted it from review, or given an Approval (i.e., do not begin the consent process -- even if it is requested by the provost office -- until you receive you final IRB letter).

Questions about FERPA and permissible uses of education records may UNC-Chapel Hill HRPP SOPs be directed to the Office of University Counsel.

1.2 Research Subject to the Protection of Pupil Rights Amendment

In order to comply with the Protection of Pupil Rights Amendment (34 CFR 98.4), the following must be in place as applicable, and the investigator must document for the IRB that for research projects directly funded by the U.S. Department of Education, no student will be required, as part of any research project, to submit without prior consent to surveys, psychiatric examination, testing, or treatment, or psychological examination, testing, or treatment, in which the primary purpose is to reveal information concerning one or more of the following:

- Political affiliations or beliefs of the student or the student’s parent.
- Mental or psychological problems of the student or the student’s family.
- Sex behavior or attitudes.
- Illegal, anti-social, self-incriminating, or demeaning behavior. Critical appraisals of other individuals with whom respondents have close family relationships.
- Legally recognized privileged or analogous relationships, such as those of lawyers, physicians, and ministers.
- Religious practices, affiliations, or beliefs of the student or student’s parent.
- Income (other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under such program).

Prior consent means prior consent of the student, if the student is an adult or emancipated minor; or prior written consent of the parent or guardian, if the student is an unemancipated minor.

1.2.1 Research Conducted in a School Receiving U.S. Department of Education Funding (34 CFR 98, 99)

For research not directly funded by the U.S. Department of Education but conducted in a school that receives funding from the U.S. Department of Education, the research protocol must include provisions, as applicable, to ensure:

- The right of a parent of a student to inspect, upon the request of the parent, a survey created by a third party before the survey is administered or distributed by a school to a student. Such access must be made available within a reasonable period of time after the request is made by the parent.
• The protection of student privacy and data confidentiality in the event of the administration or distribution of a survey to a student containing one or more of the following items (including the right of a parent of a student to inspect, upon the request of the parent, any survey containing one or more of such items):
  • Political affiliations or beliefs of the student or the student’s parent.
  • Mental or psychological problems of the student or the student’s family.
  • Sex behavior or attitudes.
  • Illegal, anti-social, self-incriminating, or demeaning behavior.
  • Critical appraisals of other individuals with whom respondents have close family relationships.
  • Legally recognized privileged or analogous relationships, such as those of lawyers, physicians, and ministers.
  • Religious practices, affiliations, or beliefs of the student or the student’s parent.
  • Income (other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under such program).

• The right of a parent of a student to have reasonable access to inspect any instructional material used as part of the educational curriculum for the student. The procedures for granting such a request must be described.

• The school has adopted a policy in conjunction with parents regarding:
  • Administration of physical examinations or screenings that the school or agency may administer to a student.
    • The collection, disclosure, or use of personal information collected from students for the purpose of marketing or for selling that information (or otherwise providing that information to others for that purpose), including arrangements to protect student privacy that are provided by the agency in the event of such collection, disclosure, or use.
  • The right of a parent of a student to inspect, upon the request of the parent, any instrument used in the collection of personal information before the instrument is administered or distributed to a student.
  • Any applicable procedures for granting a request by a parent for reasonable access to such instrument within a reasonable period of time after the request is received.

• Research Funded by the National Institute on Disability and Rehabilitation Research (34 CFR 350.4(c)(2))

When research is funded by the National Institute on Disability and Rehabilitation Research and the IRB reviews research that purposefully requires inclusion of children with disabilities or
individuals with mental disabilities as research participants, the IRB must include at least one person primarily concerned with the welfare of these research participants.
1 Research Subject to U.S. Department of Energy Regulations

When following Department of Energy (DOE) regulations, the IRB reviews and approves the “DOE Institutional Review Board Template for Reviewing Human Subjects Research Protocols that Utilize Personally Identifiable Information (PII)” submitted by the researchers to verify compliance with the DOE requirements for the protection of personally identifiable information.

Investigators must promptly (no longer than within 30 days) report the following to the human subject research program manager:

- Any significant adverse events, unanticipated risks, and complaints about the research, with a description of any corrective actions taken or to be taken.
- Any suspension or termination of IRB approval of research.
- Any significant non-compliance with HRPP procedures or other requirements.
- The time frame for “promptly” is defined.
- Any compromise of personally identifiable information must be reported immediately.
- The time frame for “immediately” is defined.
1 Case Reports Requiring IRB Review

In general, an anecdotal report on one or a series of patients seen in one’s own practice and a comparison of these patients to existing reports in the literature is not research and does not require IRB approval. Going beyond one’s own practice to seek out and report cases seen by other clinicians creates the appearance of a systematic investigation with the intent to contribute to generalizable knowledge and therefore is considered research and would require IRB approval.

1.1 Definitions

Single Case Report. The external reporting (e.g., publication, poster or oral presentation) of an interesting clinical situation or medical condition of a single patient. Case reports normally contain detailed information about an individual patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The patient information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.

Case Series. The external reporting (e.g., publication, poster or oral presentation) of an interesting clinical situation or medical condition in a series of patients (i.e., more than one patient). Case series usually contain detailed information about each patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.
Certificate of Confidentiality (CoC)

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

Generally, any research project that collects personally identifiable, sensitive information and that has been approved by an IRB operating under either an approved Federal-Wide Assurance issued by OHRP or the approval of the FDA is eligible for a Certificate. Federal funding is not a prerequisite for an NIH-issued Certificate, but the subject matter of the study must fall within a mission area of the National Institutes of Health, including its Institutes, Centers and the National Library of Medicine.

1.1 Statutory Basis for Protection

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

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

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

Any investigator engaged in research in which sensitive information is gathered from human subjects (or any person who intends to engage in such research) may apply for a CoC. Research can be considered "sensitive" if it involves the collection of:

1. Research on HIV, AIDS, and STDs;
2. Information about sexual attitudes, preferences, practices;
3. Information about personal use of alcohol, drugs, or other addictive products;
4. Information about illegal conduct;
5. Information that could damage an individual's financial standing, employability, or reputation within the community;
6. Information in a subject's medical record that could lead to social stigmatization or discrimination; or
7. Information about a subject's psychological well-being or mental health.
8. Genetic studies, including those that collect and store biological samples for future use;

This list is not exhaustive. Investigators contemplating research on a topic that might qualify as sensitive should contact the IRB Office for help in applying for a certificate.

In the consent process and form, investigators should tell research subjects that a CoC is in effect. Subjects should be given a fair and clear explanation of the protection that it affords, including the limitations and exceptions noted above. Every research project that includes human research subjects should explain how identifiable information will be used or disclosed, regardless of whether or not a CoC is in effect.

1.3 Limitations

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

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

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

1. The subject (or, if he or she is legally incompetent, his or her legal guardian) consents, in writing, to the disclosure of such information;

2. Authorized personnel of the Department of Health and Human Services (DHHS) request such information for audit or program evaluation, or for investigation of DHHS grantees or contractors and their employees; or

3. Release of such information is required by the federal Food, Drug, and Cosmetic Act or regulations implementing that Act.

1.4 Application Procedures

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

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

If there is an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE), the sponsor can request a CoC from the FDA.

For more information, see the NIH Certificates of Confidentiality Kiosk (http://grants.nih.gov/grants/policy/coc/index.htm).
1 Community Based Research

Community based research (CBR) is research that is conducted as an equal partnership between academic investigators and members of a community. In CBR projects, the community participates fully in all aspects of the research process. Community is often self-defined, but general categories of community include geographic community, a community of individuals with a common problem or issue, or a community of individuals with a common interest or goal.

Where research is being conducted in communities, investigators are encouraged to involve members of the community in the research process, including the design and implementation of research and the dissemination of results when appropriate. The [NC TraCS ] will assist the investigator in developing such arrangements.

https://tracs.unc.edu/docs/NC_TraCS_Institute_brochure_2016_8.5x11.pdf

The most significant community involvement is in a subset of CBR called Community Academic Resources for Engaged Scholarship (CARES) where there is an equal partnership between the academic investigators and members of a community, with the latter actively participating in all phases of the research process including the design and implementation of research and the dissemination of results when appropriate.

1.1 Community Partnerships in Research

Increasingly research design involves members of the community under study in the design and implementation of this research. These approaches include community engaged research and community based participatory research (CBPR).

Community-engaged research encourages the participation and influence of nonacademic researchers in the search for new knowledge. Community members, organizations, and researchers work together in all aspects of the research process. Community-engaged research is done with communities and not on communities. This approach to research recognizes the strengths of the community and builds on those strengths.

Health-related research studies may develop new treatments or find ways to prevent disease. But it can take years before these treatments become available in most clinics, doctors' offices, or community health centers. This is especially true for research that involves disadvantaged communities. Community-Based Participatory Research (CBPR) actively involves the community in the research process. CBPR seeks to directly benefit the public in a process that:
• Is a collaborative approach that equitably includes community members, organizations, and researchers in all aspects of the research process.
• Enhances the understanding of a mutually shared area of public health interest.
• Puts findings into action to improve the health and well-being of community members.

In CBPR, community members are also involved in getting the word out about the research and promoting the use of the research findings. This involvement can help improve the quality of life and health care in the community by putting new knowledge in the hands of those who need to make changes.

These processes may present challenges for both researchers and IRBs, including whether the community partners are subjects, members of the research team or both; what training is required; how to manage conflicts of interest; when is it appropriate to establish community advisory boards; how to solicit their input in ongoing involvement; whether and what kind of collaborative agreements are required; and how/when to disseminate results. In many cases it will not be necessary or appropriate to apply the same policies and requirements to community partners that are applied to University-based members of the research team. For example, it may be more appropriate for the principal investigator to provide training that is tailored to the role of community partners (e.g., church members, barbers, community advocates) than it is require completion of the same online CITI modules that investigators complete.

Outreach to the community is conducted in collaboration with the TraCS Institute, including presentations and training to community groups, provision of educational material and community events/health fairs. Feedback is obtained from participants at the conclusion of each training session. These activities are periodically evaluated in conjunction with the TraCS Institute to assess effectiveness of the program and for planning of additional offerings.

1.2 IRB Review

Questions to be considered as CBR studies are developed, and issues that the IRB will consider when reviewing CBR are as follows:

• How was the community involved or consulted in defining the need for the proposed research (i.e., getting the community’s agreement to conduct the research)?
• How was the community involved or consulted in generating the study research plan?
• How will the research procedures, including recruitment strategies and consent processes be assessed to ensure sensitivity and appropriateness to various communities (e.g., literacy issues, language barriers, cultural sensitivities, etc.)?
• How will the community be involved in the conduct of the proposed research?
• How will community members who participate in the implementation of the research be trained and supervised?
• How have “power” relationships between investigators and community members on the research team, and in subject recruitment strategies been considered to minimize coercion and undue influence?
• What are the risks and benefits of the research for the community as a whole?
• How will boundaries between multiple roles (e.g., investigator, counselor, peer) be maintained, i.e., what happens when the investigator/research staff is the friend, peer, service provider, doctor, nurse, social worker, educator, funder, etc.)
• How will the research outcomes be disseminated to the community?
• Is there a partnership agreement or memorandum of understanding to be signed by the University of North Carolina at Chapel Hill (UNC-Chapel Hill) investigator and community partners that describes how they will work together?

When CBR studies are proposed, the above information will be included in the submission materials. When CBR studies are being reviewed, the IRB Chair will review the above information with the IRB before the IRB reviews the study. When the IRB reviews CBR studies, it will include, either as members or consultants, individuals with expertise in community based research.

1.3 Reference:

Ethical Dilemmas in Community-Based Participatory Research: Recommendations for Institutional Review Boards
Sarah Flicker, Robb Travers, Adrian Guta, Sean McDonald, and Aileen Meagher
Published online 2007 April 10. doi: 10.1007/s11524-007-9165-7.
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1 Data or Biological Sample Repositories

A repository is a collection of data or biological specimens whose organizers:

• Receive data or specimens from multiple sources
• Maintain the data or specimens over time
• Control access to and use of data or specimens by multiple individuals and/or for multiple purposes, which may evolve over time

These policies and procedures apply to both data and biological sample repositories. For simplicity, both will be referred to as samples in this document.

There are two type of repositories:

• Non-research repositories created and maintained for purposes that are totally unrelated to research. Such purposes may include diagnosis, treatment, billing, marketing, quality control, and public health surveillance.

• Research repositories created and maintained specifically for research purposes. Such purposes may include databases to identify prospective subjects, patient outcome information to evaluate treatment effectiveness, and tissues samples for future research. Non-research repositories that are altered to facilitate research (e.g., through the addition of data fields not necessary for the core purpose of the repository) are considered research repositories.

1.1 Non-research Repositories

Even though repositories were not created for research purposes, they may contain information that is of great interest to researchers. The creation (or operation) of non-research databases or repositories does not involve human subject research and does not require IRB oversight. However, IRB oversight is required for use in research of identifiable private information or identifiable human specimens from non-research databases and repositories (including data/tissue banks and registries).

• When research involves identifiable private information or identifiable human specimens each research use must receive prospective IRB review and approval and continuing IRB oversight
• Researchers should submit an application for IRB review and receive IRB approval before initiating the research.
• Where available, the application should include any available information about the circumstances under which the information or specimens were originally collected.
• Investigators who believe their research may be exempt from the human subject regulations should include a request for exemption #4 with the IRB application.
• The IRB may require researchers to obtain the informed consent of subjects for research involving information or specimens contained in non-research databases or repositories. The IRB can waive the requirement for informed consent if the research meets the criteria in the regulation.

1.2 Research Repositories

Research repositories involve three components:
• the collectors of samples;
• the storage and data management center; and
• the recipient investigators.

1.2.1 Sample collection

If the samples were collected for research purposes or are associated with information that can identify the donor, then informed consent must be obtained from the donor unless appropriately waived by the IRB.

Informed Consent information should include:
• A clear description of
  o the operation of the database;
  o the specific types of research to be conducted;
  o the conditions under which data will be released to recipient-investigators; and
  o procedures for protecting the privacy of subjects and maintaining the confidentiality of data
• A statement regarding future withdrawal of the data from the study (i.e., state whether subjects may, in the future, request that their data be destroyed or that all personal identifiers be removed from data).
  • Other information, such as the length of time that data will be stored, subjects' access to information learned from the research, and secondary uses of the samples should be considered as appropriate.

Repositories should have data submission policies to ensure that the data was collected in an ethical manner, such as informed consent and IRB approval.

• Sample Storage and Management
• Repositories should have written policies on:
Data and tissue submission requirements
Informed consent
IRB review
Physical and procedural mechanisms for the secure receipt, storage, and transmission of information and specimens

- Policies on release of information and specimens
  - Coding
  - Release of identifier
  - Certificates of Confidentiality

1.2.2 Recipient Investigators

Recipient-investigators should have a written agreement with the repository. The agreement should specify under what conditions the data is being released to the recipient-investigator(s). The terms under which the data is released determine whether the research requires IRB oversight.

1.2.3 IRB Oversight

Operation of a research repository and its data management center under the auspices of the UNC-Chapel Hill is subject to oversight by the UNC-Chapel Hill IRB. Proposals to establish a repository must be submitted to the IRB specifying the conditions under which data and specimens may be accepted and shared, and ensuring adequate provisions to protect the privacy of subjects and maintain the confidentiality of data. The IRB also reviews and approves a sample collection protocol and informed consent document for distribution to sample collectors and their local IRBs.

2. Biological Specimens

All activities involving the collection of human biological specimens for research purposes, as well as the research use of specimens collected for clinical care, must be conducted under the terms of an IRB approved research protocol. The collection and use of human biological specimens (either identifiable or de-identified) must comply with all applicable laws and regulations for research involving human biological specimens or superseding requirements.

2.1 Regulatory Oversight

Under HHS regulations, a human subject is a living individual about whom an investigator conducting research obtains

- data through intervention or interaction with the individual, or
- identifiable private information

Whether research involving biological specimens meets the definition of human subjects research is based on a) how the specimens were obtained and b) whether the specimens
include identifiable private information. If the specimens are obtained specifically for research purposes, then they have been collected through intervention or interaction with the individual and, thus, the research meets the definition of human subjects research. If the specimens were not collected for research purposes but as part of routine clinical care or other non-research purpose, then the research only meets the definition of human subjects research if the specimens include identifiable private information.

An exception to this is federally-funded research involving Newborn Blood Spots. Per the Newborn Screening Saves Lives Reauthorization Act of 2014 (Public Law No: 113-240), federally-funded research funded using newborn dried spots is considered human subjects research regardless of whether the specimens are identifiable. Further, the law eliminates the ability of the IRB to approve alterations or waivers of informed consent under 45 CFR 46.116(c) and 116(d) for research involving newborn dried blood spots.

3. Research use of cord blood from births at UNC Hospitals

According to UNC Hospitals policy (February 15, 2000), any collection for research use of placental tissue, umbilical cord tissue or cord blood from births at UNC Hospitals will require written consent of the mother. Investigators seeking to acquire such specimens for research use should prepare an IRB application including a consent form. They must also notify the Department of OB/GYN, since protocols involving obstetrical patients also require review by the OB/GYN Department Research Committee and requests for cord blood may need to be prioritized. Investigators will be responsible for making arrangements for obtaining consent and collecting the specimens.

This policy is based on the following considerations:

1. Cord blood and placental tissue are a unique source of stem cells and other biologic materials, with great therapeutic potential. Consequently there is increasing demand.

2. Certain research uses of these tissues already require informed consent. In particular, the recent designation of UNC Hospitals as a collection site for an NHLBI-sponsored Cord Blood Bank for stem cell research will result in approaching most if not all mothers for permission to collect cord blood for this purpose.

3. Certain ethnic groups do not view the placenta and placental blood as waste, but as sacred objects. Using tissues from such persons without their consent would constitute a serious violation of their rights.

FDA regulations do not apply to biological specimens unless they are gathered as part of a clinical investigation involving human subjects or being used to test a medical device. HIPAA does not cover biological specimens but does cover protected health information (PHI) linked to the specimens.

Registries are sometimes created by a public authority (e.g., the North Carolina Central Cancer Registry was created by the North Carolina Legislature, see North Carolina General Statute Chapter 130A - Article 7) If the research meets the definition of human subjects research, then all of the requirements of this document apply.
3.1 IRB Review

Research involving only biological specimens may be exempt under Exemption Category #4: “Research 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.” However, in order to qualify under this category, all of the specimens must exist prior to the research being submitted to the IRB. Additionally, this exemption cannot be applied to federally-funded research involving Newborn Blood Spots.

Non-exempt research only involving biological specimens may be eligible for expedited review if it is minimal risk and falls within one of the following categories:

- Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture [with restrictions]
- Prospective collection of biological specimens for research purposes by noninvasive means.
- Research involving materials... that have been collected, or will be collected solely for nonresearch purposes

All non-exempt research involving biological specimens that are not eligible for expedited review must be reviewed at a convened IRB meeting.

For all non-exempt research involving biological specimens, informed consent and documentation of consent is required unless waived by the IRB. Informed consent is required for all federally-funded research using Newborn Blood Spots.

3.2 Coded Human Data or Biological Specimens

The UNC-Chapel Hill IRB policy is based on the OHRP guidance document entitled, “Guidance on Research Involving Coded Private Information or Biological Specimens” (October 16, 2008 http://www.hhs.gov/ohrp/policy/cdebiol.html). This document:

1. Provides guidance as to when research involving coded private information or specimens is or is not research involving human subjects, as defined under HHS regulations for the protection of human research subjects (45 CFR part 46).
2. Reaffirms OHRP policy that, under certain limited conditions, research involving only coded private information or specimens is not human subjects research.
3. Clarifies the distinction between (a) research involving coded private information or specimens that does not involve human subjects and (b) human subjects research that is exempt from the requirements of the HHS regulations.
4. References pertinent requirements of the HIPAA Privacy Rule that may be applicable to research involving coded private information or specimens.

Note: The FDA definition of human subjects differs from the Common Rule definition. Use of coded specimens for FDA-regulated research such as research on In Vitro Diagnostic Devices
requires assessment according to the FDA regulations and guidelines. Investigators should contact the IRB office for guidance.

For purposes of this policy, coded means that: (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

Guidance:

Obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research. Obtaining identifiable private information or identifiable specimens includes, but is not limited to:

1. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to the investigator from any source; and
2. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that were already in the possession of the investigator.

In general, private information or specimens are considered to be individually identifiable when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Private information or specimens are not considered to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Research involving only coded private information or specimens (other than federally-funded research using Newborn Blood Spots) do not involve human subjects per the Common Rule definition if both of the following conditions are met:

1. The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
2. The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:

   The investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement);

In some cases an investigator who obtains coded private information or specimens about living individuals under one of the conditions cited in 2(a)-(c) above may (1) unexpectedly learn the identity of one or more living individuals, or (2) for previously unforeseen reasons now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained private information or specimens pertain, then the research activity now would involve human
subjects. Unless this human subjects research is determined to be exempt. IRB review of the research would be required. Informed consent of the subjects also would be required unless the IRB approved a waiver of informed consent.

3.3 Who Should Determine Whether Coded Private Information or Specimens Constitutes Human Subjects Research

The investigator in consultation with the IRB Chair or Director of the IRB Office will determine if the research involving coded information or specimens requires IRB review following the procedures for Human Subjects Research Determinations.

3.4 Sample Storage and Management

Repositories should have written policies on:

- Data and tissue submission requirements
- Informed consent
- IRB review
- Physical and procedural mechanisms for the secure receipt, storage, and transmission of information and specimens
- Policies on release of information and specimens
- Coding
- Release of identifier
- Certificates of Confidentiality

3.5 Recipient Investigators

Recipient-investigators should have a written agreement with the repository. The agreement should specify under what conditions the data is being released to the recipient-investigator(s). The terms under which the data is released determine whether the research requires IRB oversight.

3.6 IRB Oversight

Operation of a research repository and its data management center under the auspices of the UNC-Chapel Hill is subject to oversight by the UNC-Chapel Hill IRB. Proposals to establish a repository must be submitted to the IRB specifying the conditions under which data and specimens may be accepted and shared, and ensuring adequate provisions to protect the privacy of subjects and maintain the confidentiality of data. The IRB also reviews and approves a sample collection protocol and informed consent document for distribution to sample collectors and their local IRBs.

4. Gene manipulation in human subjects research

All research involving gene transfer into human subjects or any form of recombinant DNA research must be reviewed by the University’s Institutional Biosafety Committee in addition to IRB review. All recombinant DNA research must be reviewed and approved by the NIH’s
5. Human embryonic stem cell research

Federal regulation of human embryonic stem cell research is both complex and evolving. Research proposals that involve human embryonic stem cells must be submitted to the Embryonic Stem Cell Research and Oversight (ESCRO) committee. Not all such studies (e.g., in vitro studies or animal experimentation) constitute human subjects research requiring IRB review. Studies that do involve human subjects research as defined in the regulations should be submitted to the IRB for review, in addition to the ESCRO committee.

6. Human fetal tissue transplantation research

It is unlawful for any person to knowingly acquire, receive or transfer any human fetal tissue for valuable consideration. It is unlawful for any person to solicit or knowingly acquire, receive or accept a donation of human fetal tissue for transplantation if the tissue is obtained pursuant to an induced abortion and the donation is made pursuant to a promise that it will be transplanted to any specified individual, to a relative of the donating individual, or in valuable consideration for the costs associated with the abortion. Additionally, all other ethical and regulatory requirements for the welfare and protection of human research subjects apply to both the donors and the recipients of human tissue used in transplantation research.

Human fetal tissue may be used only if it has been obtained in accord with the following requirements: (1) the woman providing the tissue must declare in a signed written statement that she is donating the tissue without any restrictions regarding the identity of the transplant recipients and without being informed of the identity of the recipients; (2) the attending physician must declare in a signed written statement that the tissue was donated by the woman and with full disclosure with regard to the physician’s interest in the research and any known medical or privacy risks associated with the research. If the tissue is obtained pursuant to an induced abortion, the attending physician must also declare in her or his signed written statement that the consent of the women for the abortion was obtained prior to requesting or obtaining consent for the donation of the tissue, no alteration of the timing, method or procedures used to terminate the pregnancy was made solely for the purpose of obtaining the tissue; and the abortion was performed in accordance with applicable state law; and (3) the PI for the research must declare in a signed written statement that: the tissue is human fetal tissue; the tissue may have been obtained pursuant to a spontaneous or induced abortion or stillbirth; the tissue was donated for research; the investigator had provided this information to other individuals involved in the research and received written acknowledgement of the receipt of this information; and the investigator has had no influences on the decision to terminate the pregnancy.

(For more information see OHRP Guidance on “Fetal Tissue Transplantation” dated February 7, 2003.)
1 Family history research

Family research typically involves obtaining information from one family member (called a proband) about other family members (third parties). For a detailed description of family history research, see SOP 2901.

1.1 Recruitment of family members via family history research

In some cases, researchers may learn about potential subjects through family history research and wish to enroll a third party in a study. In such situations, the researcher must exercise extreme care in approaching a third party via a proband.

Under most circumstances researchers should ask the proband to discuss participation in the research study with his/her family member(s) before the researcher approaches those family members directly. Additionally, researchers should obtain consent directly from the family member(s) and not via the proband.
1 Genetic Studies

Genetic research studies may create special risks to human subjects and their relatives. These involve medical, psychosocial, legal and economic risks, such as the possible loss of privacy, insurability, and employability, change in immigration status and limits on education options, and may create a social stigma. Knowledge of one's genetic make-up may also affect one's knowledge of the disease risk status of family members.

In studies involving genetic testing, several questions need to be addressed, including:

1. Will test results be given?
2. Will disease risk be quantified, including the limits on certainty of the testing?
3. Will a change in a family relationship be disclosed, such as mistaken paternity?
4. Does the subject or family member have the option not to know the results? How will this decision be recorded?
5. Could other clinically relevant information be uncovered by the study? How will disclosure of this added information occur?
6. Do any practical limitations exist on the subject's right to withdraw from the research, withdraw data, and/or withdraw DNA?
7. Is the subject permitted to participate in the study while refusing to have genetic testing (such as in a treatment study with a genetic testing component)?

For DNA banking studies, several questions need to be addressed, including:

1. Will DNA be stored or shared? If shared, will the subject’s identity be known by the new recipient investigator?
2. Will the subject be contacted in the future by the investigator to obtain updated clinical information?
3. How can the subject opt out of any distribution or subsequent use of his/her genetic material?

2 Gene manipulation in human subjects research

All research involving gene transfer into human subjects or any form of recombinant DNA research must be reviewed by the University’s Institutional Biosafety Committee in addition to
IRB review. All recombinant DNA research must be reviewed and approved by the NIH’s Recombinant DNA Advisory Committee (RAC). The results of these additional reviews should be submitted to the IRB.

NIH guidelines on recombinant DNA and gene transfer research are available online at: http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html

3 Human embryonic stem cell research

Federal regulation of human embryonic stem cell research is both complex and evolving. Research proposals that involve human embryonic stem cells must be submitted to the Embryonic Stem Cell Research and Oversight (ESCRO) committee. Not all such studies (e.g., in vitro studies or animal experimentation) constitute human subjects research requiring IRB review. Studies that do involve human subjects research as defined in the regulations should be submitted to the IRB for review, in addition to the ESCRO committee.

4 Human fetal tissue transplantation research

It is unlawful for any person to knowingly acquire, receive or transfer any human fetal tissue for valuable consideration. It is unlawful for any person to solicit or knowingly acquire, receive or accept a donation of human fetal tissue for transplantation if the tissue is obtained pursuant to an induced abortion and the donation is made pursuant to a promise that it will be transplanted to any specified individual, to a relative of the donating individual, or in valuable consideration for the costs associated with the abortion. Additionally, all other ethical and regulatory requirements for the welfare and protection of human research subjects apply to both the donors and the recipients of human tissue used in transplantation research.

Human fetal tissue may be used only if it has been obtained in accord with the following requirements: (1) the woman providing the tissue must declare in a signed written statement that she is donating the tissue without any restrictions regarding the identity of the transplant recipients and without being informed of the identity of the recipients; (2) the attending physician must declare in a signed written statement that the tissue was donated by the woman and with full disclosure with regard to the physician’s interest in the research and any known medical or privacy risks associated with the research. If the tissue is obtained pursuant to an induced abortion, the attending physician must also declare in her or his signed written statement that the consent of the women for the abortion was obtained prior to requesting or obtaining consent for the donation of the tissue, no alteration of the timing, method or procedures used to terminate the pregnancy was made solely for the purpose of obtaining the tissue; and the abortion was performed in accordance with applicable state law; and (3) the PI for the research must declare in a signed written statement that: the tissue is human fetal tissue; the tissue may have been obtained pursuant to a spontaneous or induced abortion or stillbirth; the tissue was donated for research; the investigator had provided this information to other individuals involved in the research and received written acknowledgement of the receipt of this information; and the investigator has had no influences on the decision to terminate the pregnancy.
5. **Research use of cord blood from births at UNC Hospitals**

According to UNC Hospitals policy (February 15, 2000), any collection for research use of placental tissue, umbilical cord tissue or cord blood from births at UNC Hospitals will require written consent of the mother. Investigators seeking to acquire such specimens for research use should prepare an IRB application including a consent form. They must also notify the Department of OB/GYN, since protocols involving obstetrical patients also require review by the OB/GYN Department Research Committee and requests for cord blood may need to be prioritized. Investigators will be responsible for making arrangements for obtaining consent and collecting the specimens.

This policy is based on the following considerations:

1. Cord blood and placental tissue are a unique source of stem cells and other biologic materials, with great therapeutic potential. Consequently there is increasing demand.
2. Certain research uses of these tissues already require informed consent. In particular, the recent designation of UNC Hospitals as a collection site for an NHLBI-sponsored Cord Blood Bank for stem cell research will result in approaching most if not all mothers for permission to collect cord blood for this purpose.
3. Certain ethnic groups do not view the placenta and placental blood as waste, but as sacred objects. Using tissues from such persons without their consent would constitute a serious violation of their rights.

FDA regulations do not apply to biological specimens unless they are gathered as part of a clinical investigation involving human subjects or being used to test a medical device. HIPAA does not cover biological specimens but does cover protected health information (PHI) linked to the specimens.

Registries are sometimes created by a public authority (e.g., the North Carolina Central Cancer Registry was created by the North Carolina Legislature, see [North Carolina General Statute Chapter 130A - Article 7](http://www.ncleg.gov/Statutes/Chapter_130A-7))If the research meets the definition of human subjects research, then all of the requirements of this document apply.
1 Research in educational settings

Research conducted in established or commonly accepted educational settings that involve normal educational practices as well as research involving the use of educational tests, survey procedures, interview procedures, or the observation of public behavior is eligible for exemption from the Common Rule. However, such research sometimes raises special concerns to which the IRB must be especially attentive. One example of such a concern is the “two-hat” problem in which a researcher is also an instructor with potential coercive power or undue influence over students who are also potential research subjects. Such a situation does not automatically disqualify a project from exemption, but the IRB should be cognizant of the problems such an arrangement might create. Furthermore, even if the research is exempt, the investigator has an ethical obligation to ensure that students’ rights and welfare are respected. When educational institutions become engaged in the actual conduct of research, they are required to file an assurance in accordance with 45 CFR 46.103(a).

2 Student Research

See SOP 4601 Trainee or Student Projects Involving Human Subjects Research

3 Oral History

A decision whether oral history or other activities solely consisting of open ended qualitative type interviews are subject to the policies and regulations outlined in an institution’s FWA and DHHS regulations for the protection of human research subjects (45 CFR 46) is based on the prospective intent of the investigator and the definition of "research" under DHHS regulations at 45 CFR 46.102(d): "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

Specifically, for the purposes of this policy, the evaluation of such activities hinges upon whether:

The activity involves a prospective research plan that incorporates data collection, including qualitative data, and data analysis to answer a research question; and

The activity is 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.
In order to be subject to the UNC-Chapel Hill human research protections policies, the activity must meet both of the above standards. This determination will be made according to the procedures described in Section 5 above.

General principles for evaluating Oral History activities:

1. Oral history activities, such as open ended interviews, that ONLY document a specific historical event or the experiences of individuals without intent to draw conclusions or generalize findings do not constitute "research" as defined by DHHS regulations 45 CFR 46.

Example: An oral history video recording of interviews with holocaust survivors is created for viewing in the Holocaust Museum. The creation of the video tape does not intend to draw conclusions, inform policy, or generalize findings. The sole purpose is to create a historical record of specific personal events and experiences related to the Holocaust and provide a venue for Holocaust survivors to tell their stories.

2. Systematic investigations involving open-ended interviews that are designed to develop or contribute to generalizable knowledge (e.g., designed to draw conclusions, inform policy, or generalize findings) would constitute "research" as defined by DHHS regulations at 45 CFR 46.

Example: An open ended interview of surviving Gulf War veterans to document their experiences and to draw conclusions about their experiences, inform policy, or generalize findings.

3. Oral historians and qualitative investigators may want to create archives for the purpose of providing a resource for others to do research. Because the intent of the archive is to create a repository of information for other investigators to conduct research as defined by 45 CFR 46, the creation of such an archive would constitute research under 45 CFR 46.

Example: Open ended interviews are conducted with surviving Negro League Baseball players to create an archive for future research. The creation of such an archive would constitute research under 45 CFR part 46 because the intent is to collect data for future research.

Investigators are advised to consult with the IRB Office regarding whether their oral history project requires IRB review.

3.1 Research Subject to the Family Educational Rights and Privacy Act (FERPA)

The Family Educational Rights and Privacy Act (FERPA) protects the privacy of student education records.

The Family Educational Rights and Privacy Act (FERPA) protects the privacy of student education records. The term “education records” includes any information that directly relates to a student and is maintained by an educational institution. In general, FERPA provides that, with certain exceptions, information from a student’s education records may not be released to others, including those within the same educational institution, without the student’s or parent’s prior written consent. If the student is over 18 or enrolled in college, the student must give the
consent. If the student is under 18 and not enrolled in college, the consent must come from his or her parent. For a FERPA consent to be effective, it must:

- be in writing;
- signed and dated by the student or parent (as applicable);
- specify the records that may be disclosed;
- state the purpose of the disclosure; and
- identify the party to whom the records may be released.

Notably, FERPA does not apply to schools that do not receive funds under a program of the U.S. Department of Education (e.g., certain private or parochial schools).

Note that health records pertaining to students, which are created and maintained by an educational institution (e.g., Campus Health Services; school nurses) are covered by FERPA rather than the Health Insurance Portability and Accountability Act (HIPAA). Accordingly, educational institutions must observe the restrictions and requirements of FERPA, including obtaining a valid FERPA consent (described above) or meeting a relevant exception (described below), before such records may be released.

In the research context, information from education records may be released, without the student’s or parent’s consent, to organizations conducting studies for, or on behalf of, educational agencies or institutions, but only if the study is: (1) for developing, validating, or administering [academic] predictive tests; (2) to administer student aid programs; or (3) to improve instruction. In order to qualify for this exception, the study must be conducted in such a way that parents and students may not be personally identified by anyone other than those working on the study, and the identifying information must be destroyed when it is no longer needed for the study’s purposes. If the study at issue involves the University’s data, there must be a written agreement between the University and the organization conducting the study. That agreement must:

- specify the purpose, scope and duration of the study or studies and the information to be disclosed;
- require that the organization use personally identifiable information from education records only to meet the purpose or purposes of the study as spelled out in the agreement;
- require the organization to conduct the study in such a way that there is no personal identification of parents and students by anyone other than representatives of the organization who have legitimate interests;
- require the organization to return to the University or destroy the personally identifiable information when it is no longer needed for purposes of the study; and
- specify the time period within which the organization must either return or destroy the personally identifiable information.
More generally, information from education records may be released without the student’s or parent’s consent where the information released is de-identified. Even if a student’s name or other common identifiers (e.g., date of birth, address) have been removed, the educational institution must still consider whether a reasonable person in the community could use the released information to identify a student with reasonable certainty. If so, then the information does not qualify as “de-identified” and may not be released without a valid consent.

Directory information publicly maintained by an educational institution may also be released without the student’s or parent’s consent, provided that the student or parent (as applicable) has not opted out of directory information disclosures. Researchers must check to confirm that a student has not opted out before accessing or disclosing directory information absent written consent. Researchers can verify whether a student has opted out of directory information disclosures by checking the relevant, publicly-available directory (e.g., the University’s online directory) or asking the appropriate administrative office of the educational institution (e.g., the Office of the University Registrar).

Questions about FERPA and permissible uses of education records may be directed to the Office of University Counsel.

3.2 Research Subject to the Protection of Pupil Rights Amendment

In order to comply with the Protection of Pupil Rights Amendment (34 CFR 98.4), the following must be in place as applicable, and the investigator must document for the IRB that for research projects directly funded by the U.S. Department of Education, no student will be required, as part of any research project, to submit without prior consent to surveys, psychiatric examination, testing, or treatment, or psychological examination, testing, or treatment, in which the primary purpose is to reveal information concerning one or more of the following:

- Political affiliations or beliefs of the student or the student’s parent.
- Mental or psychological problems of the student or the student’s family.
- Sex behavior or attitudes.
- Illegal, anti-social, self-incriminating, or demeaning behavior. Critical appraisals of other individuals with whom respondents have close family relationships.
- Legally recognized privileged or analogous relationships, such as those of lawyers, physicians, and ministers.
- Religious practices, affiliations, or beliefs of the student or student’s parent.
- Income (other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under such program).

*Prior consent* means prior consent of the student, if the student is an adult or emancipated minor; or prior written consent of the parent or guardian, if the student is an unemancipated minor.
3.2.1 Research Conducted in a School Receiving U.S. Department of Education Funding (34 CFR 98, 99)

For research not directly funded by the U.S. Department of Education but conducted in a school that receives funding from the U.S. Department of Education, the research protocol must include provisions, as applicable, to ensure:

- The right of a parent of a student to inspect, upon the request of the parent, a survey created by a third party before the survey is administered or distributed by a school to a student. Such access must be made available within a reasonable period of time after the request is made by the parent.
- The protection of student privacy and data confidentiality in the event of the administration or distribution of a survey to a student containing one or more of the following items (including the right of a parent of a student to inspect, upon the request of the parent, any survey containing one or more of such items):
  - Political affiliations or beliefs of the student or the student’s parent.
  - Mental or psychological problems of the student or the student’s family.
  - Sex behavior or attitudes.
  - Illegal, anti-social, self-incriminating, or demeaning behavior.
  - Critical appraisals of other individuals with whom respondents have close family relationships.
  - Legally recognized privileged or analogous relationships, such as those of lawyers, physicians, and ministers.
  - Religious practices, affiliations, or beliefs of the student or the student’s parent.
  - Income (other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under such program).

- The right of a parent of a student to have reasonable access to inspect any instructional material used as part of the educational curriculum for the student. The procedures for granting such a request must be described.
- The school has adopted a policy in conjunction with parents regarding:
  - Administration of physical examinations or screenings that the school or agency may administer to a student.
    - The collection, disclosure, or use of personal information collected from students for the purpose of marketing or for selling that information (or otherwise providing that information to others for that purpose), including arrangements to protect student privacy that are provided by the agency in the event of such collection, disclosure, or use.
  - The right of a parent of a student to inspect, upon the request of the parent, any instrument used in the collection of personal information before the instrument is administered or distributed to a student.
- Any applicable procedures for granting a request by a parent for reasonable access to such instrument within a reasonable period of time after the request is received.

- Research Funded by the National Institute on Disability and Rehabilitation Research (34 CFR 350.4(c)(2))

When research is funded by the National Institute on Disability and Rehabilitation Research and the IRB reviews research that purposefully requires inclusion of children with disabilities or individuals with mental disabilities as research participants, the IRB must include at least one person primarily concerned with the welfare of these research participants.
1 Internet research

The vast amount of social and behavioral information potentially available on the Internet has made it an important tool for researchers wishing to study the dynamics of human interactions and their consequences in this virtual medium. Researchers can potentially collect data from widely dispersed populations at relatively low cost and in less time than similar efforts in the physical world. However, the problem of subject identification and verification can severely limit this potential. For example, researchers could unknowingly involve protected populations or decisionally impaired subjects in the research study. There are also online data integrity issues.

Internet research protocols may involve research on the topic of the internet, research collecting data over the internet, observations of human behaviors on the internet, or some combination of these aspects. In evaluating studies utilizing the internet as a research tool, the IRB should ensure that investigators have a plan for:

- Obtaining and verifying informed consent if required, including parental permission and child assent; and
- Maintaining the promised degree of privacy of subjects and confidentiality of information through the use of appropriate security measures; and
- Ensuring appropriate online data collection method and data validation checks.
1 Mandatory Reporting

While any person may make a report if they have reasonable cause to believe that a child or elder was abused or neglected, North Carolina law mandates that certain persons who suspect child or elder abuse or neglect report this as outlined below.

The UNC-Chapel Hill policy requires the solicitation of informed consent from all adult research subjects and, where appropriate, assent from children involved as research subjects, in addition to the permission of their parents. In situations where conditions of abuse or neglect might be revealed, mandated reporters should make themselves known as such to parents of children under age 18, to subjects who are children, and to subjects who are potential victims of abuse or neglect.

A principal investigator (PI) or other researcher may encounter a participant in a research study or clinical trial who the PI or researcher believes may have a condition that is required to be reported to a state-wide official. Generally, if the participant is within a protected category – based on age or mental or physical condition – or if the condition may threaten the public health, then the researcher will have a duty to report to a designated official in North Carolina. The purpose of this memo is to outline those situations in which a PI or researcher has a duty to report, and clarify to whom the report must be made.

1.1 Required Reporting

1.1.1 Dependency, Abuse, or Neglect Regarding Children or Minors

If a study participant is less than 18 years of age, and the PI or researcher has cause to suspect that the minor participant is dependent, abused or neglected by a parent, guardian,

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1 “Dependent” is defined as in need of assistance or placement because the child has no parent, guardian, or custodian responsible for the child’s care or supervision or whose parent, guardian, or custodian is unable to provide for the care of supervision and lacks an appropriate alternative child care arrangement. NCGS §7B-101(9).

2 “Abuse” has a multi-part definition that includes intentional serious physical injury, creation of a substantial risk of serious physical injury or emotional damage, cruel or grossly inappropriate procedures, criminal sex acts, and encouragement or approval of acts of delinquency or moral turpitude. NCGS §7B-101(1).

3 “Neglected” is defined as not receiving proper care, supervision, or discipline; abandoned; not provided necessary medical care or remedial care; living in an environment injurious to the child’s welfare; or placed for care or adoption in violation of law. NCGS §7B-101(15).
custodian, or caretaker\textsuperscript{4}, or that the participant has died as the result of maltreatment from a parent, guardian, custodian, or caretaker, then the PI or researcher must report the case of the participant to the Director of the Department of Social Services in the county where the child resides or is found. Under the statute, the abuse or neglect must be from a parent, guardian, custodian, or caretaker in order to be reportable. The PI or researcher may make the report orally, by telephone, or writing. If the report is made either orally or by telephone, the person making the report must give his/her name, address, and telephone number. The report must include the following items of information as known:

- Name of the child;
- Address of the child;
- Name of the parent, guardian or caretaker;
- Address of the parent, guardian, or caretaker;
- Age of the child;
- Names and ages of other children in the home;
- Present whereabouts of the child if not at the home address;
- Nature and extent of any injury or condition resulting from abuse, neglect, or dependency;
- Any other information which the person making the report believes might be helpful in establishing the need of protective services or court intervention.\textsuperscript{5}

Anyone who makes a report as outlined above, who cooperates with the county DSS in a protective services inquiry or investigation, who testifies in any judicial proceeding resulting from a protective services report or investigation, or who otherwise participates in the program authorized by the law is immune from any civil or criminal liability that might otherwise be incurred or imposed for that action, provided that the person was acting in good faith.\textsuperscript{6}

\subsection*{1.1.2 Disabled Adults}

If a PI or researcher has a study participant who is 18 years of age or over or who is an emancipated minor, and who is also physically or mentally incapacitated due to:

- mental retardation, cerebral palsy, epilepsy or autism,
- organic brain damage caused by advanced age or other physical degeneration in connection therewith, or
- conditions incurred at any age which are the result of accident, organic brain damage, mental or physical illness, or continued consumption or absorption of substances,

\footnote{\textsuperscript{4} “Caretaker” is defined as any person other than a parent, guardian, or custodian who has responsibility for the health and welfare of a juvenile in a residential setting. This definition includes stepparent, foster parents, adult members of the juvenile’s household, adult relatives entrusted with the juvenile’s care, house parents or cottage parents in a residential child care facility or residential educational facility, and any employee or volunteer of a division, institution or school operated by the NC DHHS. The definition also includes any person who has the responsibility for the care of a juvenile in a child care facility. NCGS §7B-101(3).}

\footnote{\textsuperscript{5} NCGS §7B-301.}

\footnote{\textsuperscript{6} NCGS §7B-309.}
• and the PI or researcher has reasonable cause to believe that the disabled adult is in need of protective services due to abuse\(^7\) or neglect\(^8\) by a caretaker, then the PI or researcher must report such information to the Director of the Department of Social Services in the county where the disabled adult resides or is found.

The report may be made orally or in writing. The report must include:

- Name of the disabled adult;
- Address of the disabled adult;
- Name of the disabled adult’s caretaker;
- Address of the disabled adult’s caretaker;
- Age of the disabled adult;
- The nature and extent of the disabled adult’s injury or condition resulting from abuse or neglect;
- Other pertinent information.\(^9\)

Anyone who makes a report as outlined above, who testifies in any judicial proceeding resulting from a protective services report or investigation, or who participates in a required evaluation is immune from any civil or criminal liability on account of such report or testimony or participation, unless the person acted in bad faith or with a malicious purpose.\(^10\)

### 1.1.3 Persons with a Communicable Disease

Apart from the general reporting requirements described already in this memo that apply to any person working on a research study or clinical trial, there are particular reporting requirements applicable to principal investigators or researchers who are licensed physicians. Specifically, a physician licensed to practice medicine who has reason to suspect that a person about whom the physician has been consulted professionally has a communicable disease\(^11\) or communicable condition\(^12\) declared by the Commission for Health Services (Commission) to be reported, must report information required by the Commission to the local health director of

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7  “Abuse” is defined as the willful infliction of physical pain, injury, or mental anguish, unreasonable confinement, or the willful deprivation by a caretaker of services which are necessary to maintain mental and physical health. NCGS §108A-101(a).

8  “Neglect” refers to a disabled adult who is either living alone and not able to provide for himself the services which are necessary to maintain his mental or physical health or is not receiving services from his caretaker. A person is not receiving services from his caretaker if, among other things and not by way of limitation, he is a resident of one of the State-owned hospitals for the mentally ill, centers for the mentally retarded or North Carolina Special Care Center he is, in the opinion of the professional staff of that hospital or center, mentally incompetent to give his consent to medical treatment, he has no legal guardian or other guardian, and he needs medical treatment. NCGS §108A-101(m).

9  NCGS §108A-102(b).

10 NCGS §108A-102(c).

11 “Communicable disease” is defined as an illness due to an infectious agent or its toxic products which is transmitted directly or indirectly to a person from an infected person or animal through the agency of an intermediate animal, host or vector, or through the inanimate environment. NCGS §130A-133(1).

12 “Communicable condition” is defined as the state of being infected with a communicable agent but without symptoms. NCGS §130A-133(5).
the county or district in which the physician is consulted.\textsuperscript{13} Reportable conditions can be found online at \url{http://epi.publichealth.nc.gov/cd/}. The site lists more than sixty conditions. It is important to note that, by statute, HIV infection is a reportable communicable condition.\textsuperscript{14}

While not mandatory, a medical facility in which there is a patient reasonably suspected of having a communicable disease or condition declared by the Commission to be reported, may report information specified by the Commission to the local health director of the county or district in which the facility is located.

1.2 Conclusion

Any researcher working on a research study or clinical trial should ensure that he/she is aware of the statewide reporting requirements as they are applicable to the study. This memo is designed to provide a general overview of those requirements and to emphasize that if a researcher makes a report based upon reasonable cause then he/she will be protected from liability.

If you have any additional questions, you should feel free to contact the Office of University Counsel.

Investigators should consult these sources to determine if potential subjects should be advised of mandatory reporting requirements during the informed consent process.

\textsuperscript{13} This mandatory reporting requirement also applies to principals and operators of child care facilities (child care centers, family child care homes, and any other child care arrangement – although not public schools – that provide child care, regardless of the time of day, wherever operated, and whether or not operated for profit).

\textsuperscript{14} NCGS §130A-135.
Multi-site studies where UNC-Chapel Hill is the lead coordinating center

This scenario arises when:

- UNC-Chapel Hill is the lead coordinating center responsible for overall study conduct; or
- A UNC-Chapel Hill employee serves as principal investigator for the entire multi-site study, (unless coordinating function located elsewhere as in some NIH-sponsored groups), or
- UNC-Chapel Hill is the sponsor (initiates contracts with and disburses funds to other sites).

Under these circumstances, the UNC-Chapel Hill PI has additional responsibilities beyond those for a single site study which include notifying the UNC-Chapel Hill IRB of the multi-site nature of the study. The Lead Site/Coordinating Center Investigator Responsibilities addendum should be completed when UNC-Chapel Hill is the lead site or coordinating center for a multi-site study.

The UNC-Chapel Hill PI is responsible for the management of information that is relevant to the protection of subjects for activities that do not occur at UNC, such as:

- Unanticipated problems involving risks to subjects or others,
- Interim results,
- Protocol modification

This information is captured in the Protocol Addendum: The Lead Site/Coordinating Center Investigator Responsibilities addendum.

When the UNC investigator is the lead investigator of a multi-center study, the IRB evaluates whether the management of information that is relevant to the protection of subjects is adequate. In addition, the PI should notify the Office of Sponsored Research or the Office of Clinical Trials when the project is externally funded. If there is a contractual agreement between UNC-Chapel Hill and the research site(s) the contract should address the responsibilities described in this addendum.

For such multi-site studies, it is the responsibility of the UNC-Chapel Hill PI to provide to the UNC-Chapel Hill IRB assurance that the study at that site will be conducted in compliance with federal regulations (including 45 CFR 46 and HIPAA), all applicable state and local regulations, and ethical principles governing research involving human subjects. Each site must have IRB approval for the study whether by the site’s IRB or by an external IRB before the study can be conducted at that site. For studies that are federally funded it may be necessary for each site to have its own Federalwide Assurance (FWA) with OHRP, depending on the

In many cases, investigators at an FWA institution will have a local IRB to which they are responsible; if no such affiliation exists, then the UNC-Chapel Hill IRB may serve as the IRB of record for that investigator. These agreements should be negotiated at the time of initial review or as sites are added (See SOP 901 for more information).

The UNC-Chapel Hill PI is responsible for collecting and maintaining documentation of IRB approvals at each of the participating sites. Submission of these approvals and related documents (e.g., consent forms for participating sites) to the UNC-Chapel Hill IRB is not required, unless requested.

The UNC-Chapel Hill PI is responsible for developing a Data and Safety Monitoring Plan and for implementing a system for reporting and reviewing all unanticipated problems (UP) and adverse events (AEs). If the IRB deems formal oversight by an independent Data and Safety Monitoring Board (DSMB) to be necessary and there is no external DSMB provided, the IRB may require oversight by a UNC-Chapel Hill DSMB.
1 Oral History

A decision whether oral history or other activities solely consisting of open ended qualitative type interviews are subject to the policies and regulations outlined in an institution’s FWA and DHHS regulations for the protection of human research subjects (45 CFR 46) is based on the prospective intent of the investigator and the definition of "research" under DHHS regulations at 45 CFR 46.102(d): "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

Specifically, for the purposes of this policy, the evaluation of such activities hinges upon whether:

The activity involves a prospective research plan that incorporates data collection, including qualitative data, and data analysis to answer a research question; and

The activity is 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.

In order to be subject to the UNC-Chapel Hill human research protections policies, the activity must meet both of the above standards. General principles for evaluating Oral History activities:

1. Oral history activities, such as open ended interviews, that ONLY document a specific historical event or the experiences of individuals without intent to draw conclusions or generalize findings do not constitute "research" as defined by DHHS regulations 45 CFR 46.

Example: An oral history video recording of interviews with holocaust survivors is created for viewing in the Holocaust Museum. The creation of the video tape does not intend to draw conclusions, inform policy, or generalize findings. The sole purpose is to create a historical record of specific personal events and experiences related to the Holocaust and provide a venue for Holocaust survivors to tell their stories.

2. Systematic investigations involving open-ended interviews that are designed to develop or contribute to generalizable knowledge (e.g., designed to draw conclusions, inform policy, or generalize findings) would constitute "research" as defined by DHHS regulations at 45 CFR 46.

Example: An open ended interview of surviving Gulf War veterans to document their experiences and to draw conclusions about their experiences, inform policy, or generalize findings.

3. Oral historians and qualitative investigators may want to create archives for the purpose of providing a resource for others to do research. Because the intent of the archive is to create
a repository of information for other investigators to conduct research as defined by 45 CFR 46, the creation of such an archive would constitute research under 45 CFR 46.

Example: Open ended interviews are conducted with surviving Negro League Baseball players to create an archive for future research. The creation of such an archive would constitute research under 45 CFR part 46 because the intent is to collect data for future research.

Investigators are advised to consult with the IRB Office regarding whether their oral history project requires IRB review.
Pilot studies

A pilot study is typically defined as an initial or smaller-scale investigation or a study to either test out new experimental designs (including survey or instrument development) or methods of treatment. Pilot studies are synonymous with feasibility studies, where the investigation proposed is planned to identify various issues (e.g., relating to design of an instrument, analysis of power concerns and recruitment strategies) to determine that the larger study of the same subject matter has the greatest potential to successfully test the intended research hypotheses. Pilot studies involving human subjects are considered human subject research and require IRB review. A researcher planning to conduct a pilot study must provide sufficient details to address how a smaller scale investigation is worth pursuing with a goal of obtaining results that may add to the generalizable knowledge while minimizing any anticipated risks to the subjects. There must be a well-detailed literature review and the researcher must justify the need for the number of subjects required.
1 Qualitative research

Qualitative studies, which may involve such methods as participant observation, case studies, unstructured interviews, focus groups and various other descriptive techniques, raise special issues for the IRB. Qualitative research investigators usually have a well-articulated plan for their research, often have one or more reasonably specific hypotheses to be tested, and can describe in general terms the techniques they intend to employ. However, they may undertake research projects with the full expectation that techniques will be developed in the course of research, used on the basis of opportunity, and modified as events and experiences suggest are necessary for the success of the project. As a result, qualitative research investigators may present a research protocol that does not fit the usual model contemplated by federal human subject regulations for research, if those regulations are narrowly interpreted.

Reviewing qualitative research projects requires flexibility on the part of the IRB and is facilitated by a willingness to waive some of the elements of informed consent and approve methods of consent that are culturally appropriate. If the study protocol approved by the IRB is intended to encompass development of one or more research instruments, it may also be necessary to give relatively wide professional latitude to scientists in the application of approved methods so that an investigator does not need to come back to the IRB repeatedly for approval of changes that would be considered normal and routine under the circumstances. However, the IRB should make clear to the investigator that any significant changes, including all changes that could increase risk for the human subjects (for example, the addition of a new topic in a survey), must be approved in advance by the IRB.

Finally, the IRB may need to consider an informed consent process that is multi-layered and takes place over time as the research develops and the investigator is better able to articulate both areas of further interest and the methods being employed for studying them. Whatever flexibility the IRB decides is appropriate in the specific research context, that determination must include adequate protection for the welfare and rights of the human subjects in that specific context.
1  Research Involving Coded Private Information or Biological Specimens

1.1 Biological Specimens

All activities involving the collection of human biological specimens for research purposes, as well as the research use of specimens collected for clinical care, must be conducted under the terms of an IRB approved research protocol. The collection and use of human biological specimens (either identifiable or de-identified) must comply with all applicable laws and regulations for research involving human biological specimens or superseding requirements.

1.2 Regulatory Oversight

Under HHS regulations, a human subject is a living individual about whom an investigator conducting research obtains

- data through intervention or interaction with the individual, or
- identifiable private information

Whether research involving biological specimens meets the definition of human subjects research is based on a) how the specimens were obtained and b) whether the specimens include identifiable private information. If the specimens are obtained specifically for research purposes, then they have been collected through intervention or interaction with the individual and, thus, the research meets the definition of human subjects research. If the specimens were not collected for research purposes but as part of routine clinical care or other non-research purpose, then the research only meets the definition of human subjects research if the specimens include identifiable private information (See below for policies on coded specimens).

An exception to this is federally-funded research involving Newborn Blood Spots. Per the Newborn Screening Saves Lives Reauthorization Act of 2014 (Public Law No: 113-240), federally-funded research funded using newborn dried spots is considered human subjects research regardless of whether the specimens are identifiable. Further, the law eliminates the ability of the IRB to approve alterations or waivers of informed consent under 45 CFR 46.116(c) and 116(d) for research involving newborn dried blood spots.
1.3 Research use of cord blood from births at UNC Hospitals

According to UNC Hospitals policy (February 15, 2000), any collection for research use of placental tissue, umbilical cord tissue or cord blood from births at UNC Hospitals will require written consent of the mother. Investigators seeking to acquire such specimens for research use should prepare an IRB application including a consent form. They must also notify the Department of OB/GYN, since protocols involving obstetrical patients also require review by the OB/GYN Department Research Committee and requests for cord blood may need to be prioritized. Investigators will be responsible for making arrangements for obtaining consent and collecting the specimens.

This policy is based on the following considerations:

1. Cord blood and placental tissue are a unique source of stem cells and other biologic materials, with great therapeutic potential. Consequently there is increasing demand.

2. Certain research uses of these tissues already require informed consent. In particular, the recent designation of UNC Hospitals as a collection site for an NHLBI-sponsored Cord Blood Bank for stem cell research will result in approaching most if not all mothers for permission to collect cord blood for this purpose.

3. Certain ethnic groups do not view the placenta and placental blood as waste, but as sacred objects. Using tissues from such persons without their consent would constitute a serious violation of their rights.

FDA regulations do not apply to biological specimens unless they are gathered as part of a clinical investigation involving human subjects or being used to test a medical device. HIPAA does not cover biological specimens but does cover protected health information (PHI) linked to the specimens.

Registries are sometimes created by a public authority (e.g., the North Carolina Central Cancer Registry was created by the North Carolina Legislature, see North Carolina General Statute Chapter 130A - Article 7) If the research meets the definition of human subjects research, then all of the requirements of this document apply.

1.4 IRB Review

Research involving only biological specimens may be exempt under Exemption Category #4: “Research 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.” However, in order to qualify under this category, all of the specimens must exist prior to the research being submitted to the IRB. Additionally, this exemption cannot be applied to federally-funded research involving Newborn Blood Spots.

Non-exempt research only involving biological specimens may be eligible for expedited review if it is minimal risk and falls within one of the following categories:
• (2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture [with restrictions]
• (3) Prospective collection of biological specimens for research purposes by noninvasive means.
• (5) Research involving materials... that have been collected, or will be collected solely for non-research purposes

All non-exempt research involving biological specimens that are not eligible for expedited review must be reviewed at a convened IRB meeting.

For all non-exempt research involving biological specimens, informed consent and documentation of consent is required unless waived by the IRB. Informed consent is required for all federally-funded research using Newborn Blood Spots.

1.5 Coded Human Data or Biological Specimens

The UNC-Chapel Hill IRB policy is based on the OHRP guidance document entitled, “Guidance on Research Involving Coded Private Information or Biological Specimens” (October 16, 2008 http://www.hhs.gov/ohrp/policy/cdebiol.html). This document:

1. Provides guidance as to when research involving coded private information or specimens is or is not research involving human subjects, as defined under HHS regulations for the protection of human research subjects (45 CFR part 46).
2. Reaffirms OHRP policy that, under certain limited conditions, research involving only coded private information or specimens is not human subjects research.
3. Clarifies the distinction between (a) research involving coded private information or specimens that does not involve human subjects and (b) human subjects research that is exempt from the requirements of the HHS regulations.
4. References pertinent requirements of the HIPAA Privacy Rule that may be applicable to research involving coded private information or specimens.

Note: The FDA definition of human subjects differs from the Common Rule definition. Use of coded specimens for FDA-regulated research such as research on In Vitro Diagnostic Devices requires assessment according to the FDA regulations and guidelines. Investigators should contact the IRB office for guidance.

For purposes of this policy, coded means that: (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.
Guidance:

Obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research. Obtaining identifiable private information or identifiable specimens includes, but is not limited to:

1. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to the investigator from any source; and

2. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that were already in the possession of the investigator.

In general, private information or specimens are considered to be individually identifiable when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Private information or specimens are not considered to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Research involving only coded private information or specimens (other than federally-funded research using Newborn Blood Spots) do not involve human subjects per the Common Rule definition if both of the following conditions are met:

1. The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and

2. The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
   - The investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement);
   - There are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
   - There are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

In some cases an investigator who obtains coded private information or specimens about living individuals under one of the conditions cited in 2(a)-(c) above may (1) unexpectedly learn the identity of one or more living individuals, or (2) for previously unforeseen reasons now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained private
information or specimens pertain, then the research activity now would involve human subjects. Unless this human subjects research is determined to be exempt, IRB review of the research would be required. Informed consent of the subjects also would be required unless the IRB approved a waiver of informed consent.

1.6 Who Should Determine Whether Coded Private Information or Specimens Constitutes Human Subjects Research

The investigator in consultation with the IRB Chair or Director of the IRB Office will determine if the research involving coded information or specimens requires IRB review following the procedures for Human Subjects Research Determinations.
1 Research involving deception or withholding of information

Some research designs may require the withholding of information from human subjects. Research involving deception or withholding of information must be reviewed by the IRB with common sense and sensitivity. The withholding of information by researchers is different from the practice of deception, in which researchers provide false or misleading information to subjects. Studies involving deception need to be carefully reviewed by the IRB to ensure that the deception is justified through an examination of the risks and benefits of that deception. Furthermore, the IRB should ensure that, when appropriate, the subjects will be debriefed. Before approving a study that involves deception, the IRB should determine that the subject population is suitable and that the deception involved in the study would not alter a subject’s assessment of risk to himself/herself if he/she was aware of the deception at the time he/she agreed to participate.

Deception can only be permitted where the IRB finds and documents that waiver or alteration of the informed consent requirements is justified according to 45 CFR 46.116(d). The IRB must document that the following criteria have been satisfied:

- 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 with additional pertinent information after participation.
1 Research involving potentially addictive substances

With respect to cigarettes and alcoholic beverages, IRBs and researchers should be aware that under North Carolina state law these substances may not be distributed to or used by minors.

When research involving potentially addictive substances is proposed, the IRB must consider the subjects’ capacity to provide ongoing informed consent if judgment is diminished by exposure to the substances. There may also be unusual potential for coercion in some circumstance, for example if such research involves subjects that are institutionalized.

The IRB must also be sensitive to the ethical context of the research, in that there may be other ethical dilemmas associated with these studies if they involve the use of deception or include randomization. It is critical that the IRB focus on the considerations of risk and benefit of such research.

In addition, research involving substances that may impair the judgment of subjects must include provisions for the safety of those subjects both within the research setting and if those subjects choose to withdraw from research while in an impaired state. For example, if a subject who is legally intoxicated should choose to withdraw from a study, he or she cannot be permitted to drive from the research setting.

Potential human subjects with a history of addiction or with direct access to the class of substances in their work environment should be excluded from studies using potentially addictive substance, unless the IRB makes a determination that there is a compelling reason for their inclusion and the study includes all appropriate safeguards to reduce the risk for these subjects.
1 Research involving radiation

Studies involving the use of radiation, such as those requiring patients to be X-rayed, are not eligible for expedited review, even if all of the other procedures in the study have been deemed to pose no more than minimal risk.

Projects in which subjects are exposed to ionizing radiation must receive approval from the Radiation Safety Subcommittee (RSS) of UNC-Chapel Hill before final IRB approval can be granted. The Application for Human Use of Radiation in Research should be completed and approved by the Radiation Safety Subcommittee prior to submitting to the IRB.

However, if subjects are 18 years and older and receiving five or fewer of the following views/scans, the RSS has determined that they represent no greater than minimal risk and therefore do not require review and approval by the RSS.

- DEXA scans
- Chest x-rays
- Planar x-rays of extremities (as defined by Nuclear Regulatory Commission) – hands, forearms, elbows, feet, knees, leg below the knees, and ankles
- Dental x-rays

It is important to note that one procedure could have multiple views/scans (e.g., AP and Lat view for “chest x-ray”). The following statement must be included in the risk section of the consent form:

This research study involves exposure to radiation from (insert maximum number scans and type of procedure). Please note that this radiation exposure is not necessary for your medical care and is for research purposes only.

For comparison, the average person in the United States receives a radiation exposure of 0.3 rem (or 300 mrem) per year from natural background sources, such as from the sun, outer space, and from radioactive materials that are found naturally in the earth’s air and soil. The dose that you will receive from participation in this research study is less than amount you receive from these natural sources in one year.

The amount of radiation you will receive in this study has a minimal risk and is below the dose guideline established by The University of North Carolina Radiation Safety Committee for research subjects.
For studies that meet the criteria for approval by the Radioactive Drug Research Committee (RDRC), investigators should also submit a UNC RDRC Application. Such studies must be basic research and meet limits on pharmacological dose and radiation dose as specified in the RDRC regulations (21 CFR 361.1).
1 Research using existing data and materials

Each separate human subjects research study requires IRB review and approval of the specific proposed study, regardless of whether the data set or research materials have been previously compiled.

Research involving the use of data meeting any one of the conditions below is not considered human subjects research and does not require approval by the IRB:

- Data on decedents;
- Data that have been stripped of all identifiers that could link that data to living persons;
- Data coded in such a way that the present investigators cannot identify individual subjects (e.g., access to linkage codes is prohibited through an agreement with the custodian).

Under federal regulations, research utilizing only the types of data described above is not considered human subjects research and need not be approved by the IRB, although IRB review may be needed to make this determination.

Research involving the use of data meeting one of the conditions below is eligible for IRB exemption from continuing review:

- If the sources of data are publicly available; (45 CFR 46.101(b)(4))
- 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. (45 CFR 46.101(b)(4))

When existing data sets contain identifiable private information about living individuals and these sets are not publicly available, IRB review and approval is required before research can proceed. The IRB must determine whether the information can be used without obtaining additional informed consent. As such, the IRB should first examine the conditions of informed consent under which the data were originally obtained. It may be that the proposed research is permissible under the conditions under which the data were obtained, including contracts, informed consent or a HIPAA authorization.

If this is not the case, the IRB should consider whether it is appropriate to waive the informed consent requirements in accordance with 45 CFR 46.116(d). In many cases, a waiver of consent will be appropriate. In other cases, the IRB may determine that the research can only proceed if the investigator obtains data with codes and identifiers removed in such a way as to preclude the investigator or the source maintaining the data set from establishing subjects’ identities. If the proposed data set includes PHI the IRB must determine whether the original HIPAA
authorization will cover the use of the data, whether the IRB can waive authorization or whether additional consent/authorization is required.

Prospective studies using materials (e.g., data, documents, records, specimens) that will be collected for some purpose unrelated to the research do not qualify for exemption. The IRB may use expedited procedures to review research that proposes to use materials (e.g., data, documents, records, specimens) that will be collected in the future for non-research purposes. The IRB review should include review of the terms and conditions under which the data or materials were originally obtained and released to the investigator. The purpose of this review is to make sure that the proposed new use is not incongruent with original purposes, permissions, or approvals.
1 Review involving data from voice, video, digital or image recordings

If researchers wish to utilize data from voice, video, digital or image recordings, they must take a variety of special precautions. First, the researcher must obtain appropriate permissions from subjects who will not have their anonymity protected due to the very nature of the data being collected. The information or fact sheet and/or informed consent document must explain the intended use of the voice, video or image data, the provisions being taken for the storage of the data, and the means and timeline planned for the destruction of these data. Because of these unique constraints, researchers must take great care in authoring protocols in which the use of voice, video and image data are planned.

Certain studies involve the collection of voice, video and image data for the purpose of creating an archive or registry that will preserve the data indefinitely. In such cases, researchers will not make provisions for the destruction of data, and they should take care to inform participants of the archival nature of the data gathering performed in such a study.

1.1 PhotoVoice

Some researchers use a method of qualitative data collection in which participants take photographs of some aspect(s) of their lives, environment, or community. The photographs are then used as a basis for group discussions and to elicit important qualitative information about the photographers’ attitudes and beliefs. The degree of risk to subjects in such research depends, in part, on what is photographed. For example, this process may pose the risk of self-incrimination to subjects who photograph themselves taking part in certain activities.

From the perspective of the IRB, the “human subjects” in the research are the research participants who are taking the photographs and then presenting their interpretations in group or other data gathering sessions. If the photographers are minors, then written parental consent for their participation in the research is required, along with assent of the child participant.

Although the individuals whose photos are taken are not the subjects of the research, there may be legal requirements for obtaining permission for using their photographs. If the photographers take photos of other people, then written permission to use the photo should be obtained. If the person being photographed is a minor, then written permission to take the photo must be obtained from the child’s parent or guardian. Those being photographed must be informed about how their photo will be used, and whether they will have the opportunity to
view the photo before making a final decision about its use. If the photographs will be publicly displayed, such as at a professional meeting or community gathering, or used in manuals or brochures or other publications, then written consent to take and display the photograph publicly is required. Researchers must have a method to link pictures with the signed permission forms.
1 Survey research

The IRB should pay particular attention to the following issues in survey research:

- Possibility of undue influence in administration of the survey;
- Possibility of deductive disclosure based on demographic information garnered from subjects (subject confidentiality and privacy must be protected);
- The setting of the survey and the issues raised by such a setting; and
- The mode of obtaining consent, especially when implied consent is to be used. Surveys may often involve a waiver of written consent, and in these instances, attention should be paid to the oral presentation of required elements of consent (e.g., review of phone script for telephone surveys).
1. The UNC-Chapel Hill Students and Employees as Research Subjects

1.1 Direct appeal to students, employees or trainees

Generally, researchers at UNC-Chapel Hill may not solicit by direct appeal to students, employees or trainees in that researcher’s department or class in an effort to recruit subjects for a study. Such direct and targeted solicitation (which should be distinguished from the dissemination of information such as is done in mass distribution emails) takes place within a power dynamic that could be construed as coercive by the potential subjects being solicited. The IRB should evaluate the proposed method of recruitment as it would be applied to students, employees or trainees to make sure that recruitment materials are not presented in a manner that could suggest that their decision regarding research participation could have an effect on their relationship with instructors, mentors or employers.

When the UNC-Chapel Hill students and/or employees are being recruited as potential subjects, investigators must ensure that there are additional safeguards for these subjects. The voluntary nature of their participation must be primary and without undue influence on their decision. Investigators must emphasize to subjects that neither their academic status or grades, or their employment, will be affected by their participation decision.

To minimize coercion, investigators should avoid, whenever possible, the use of their students and employees in procedures which are neither therapeutic nor diagnostic. In these latter situations, investigators should solicit subjects through means such as bulletin board notices, flyers, advertisements in newspapers, and announcements in classes or laboratories other than their own. When entering a classroom to recruit students and conduct research, e.g., administer a survey, investigators must do so at the end of the class period to allow non-participating students the option of leaving the classroom, thereby alleviating pressure to participate.
1 **Student Research**

1.1 **Human Subject Research and Course Projects**

Learning how to conduct ethical human subject research is an important part of a student’s educational experience. Research activities that are designed as part of a course requirement for purposes of learning experience only and are not “designed to develop or contribute to generalizable knowledge” may not require IRB review. When IRB review is not required, the IRB recommends the following parameters for student research:

- Results of the research are viewed only by the course instructor for teaching purposes and discussed within the classroom for teaching and learning purposes.
- Results of the research are not made public through presentation (outside of the classroom) and are not published in paper or electronic format (e.g., available on the internet, journal publication, etc.).
- Research procedures are no more than minimal risk.
- Vulnerable populations are not targeted (e.g., children under age 18, prisoners, persons who are cognitively impaired, etc.).
- Data collected are recorded in such a manner that the subjects are not identifiable (images in videotapes and photographs and voices on audiotape are identifiable).
- When appropriate, an informed consent process is in place.

1.2 **Responsibility of the Course Instructor:**

The course instructor is responsible for communicating to the students the ethics of human subject research, for ensuring the protection of human subjects (including a process is in place for obtaining voluntary informed consent from research subjects when appropriate), and for monitoring the students’ progress.

When designing a project, students should be instructed on the ethical conduct of research and on the preparation of the IRB application when such is required. In particular, instructors and students should:

- Understand the elements of informed consent;
- Develop appropriate consent documents;
• Plan appropriate strategies for recruiting subjects;
• Identify and minimize potential risks to subjects;
• Assess the risk-benefit ratio for the project;
• Establish and maintain strict guidelines for protecting privacy and confidentiality, and
• Allow sufficient time for IRB review (if necessary) and completion of the project.

In making a determination of whether or not a class research project requires IRB review, the instructor is encouraged to contact the IRB office for assistance.

1.3 Student or trainee honors projects, theses and dissertations

Student or trainee research projects in the form of directed or independent research, such as theses, dissertations and honors research projects, are generally research intended to contribute to generalizable knowledge. When they involve human subjects, these projects require IRB review, as with any human subject research (See Appendix C).

1.4 Student or trainee human subjects projects (class projects)

Class human subject research projects (not for thesis or dissertation) are often designed primarily to educate students in research techniques or issues, without an expectation of contributing to generalizable knowledge. However, since the lines between educational goals and research are sometimes difficult to demarcate, and class projects may still (either directly or through data about them) involve living persons, class projects may expose individual subjects to the same risks as research intended for broader purposes. Furthermore, since a major goal of a class project should be to educate students in the process of human subjects research, instructors should make every effort to make the research process as realistic as possible.

1.5 Training of student researchers

Trainees must complete the human research education training required for all University research team members, or a tailored package deemed appropriate by the IRB, in consultation with the instructor. Instructors should actively instruct the students in the application of ethical principles and regulations as they apply to the class project, including, but not limited to, respect for persons as it translates into informed consent, courtesy, avoidance of unnecessary discomfort, and protection of privacy.

Students and advisors should contact the IRB Office with any questions.
1 Transnational Research

The IRB will review all transnational research involving human participants to assure adequate provisions are in place to protect the rights and welfare of the participants.

Approval of research is permitted if “the procedures prescribed by the foreign institution afford protections that are at least equivalent to those provided in 45 CFR 46.”

All policies and procedures that are applied to research conducted domestically should be applied to research conducted in other countries, as appropriate.

For transnational research, the UNC-Chapel Hill IRB seeks sufficient knowledge of the local research context by requesting approval for the project from local IRBs or ethics committees (which may or may not be OHRP-registered) and/or local letters of support. The source of this information will depend on the nature of the study, on the country and on the resources available to the investigator. Where there is a local IRB/IEC, the UNC-Chapel Hill IRB must receive and review the foreign institution or site’s IRB/IEC review and approval of each study prior to beginning the research at the foreign institution or site.

In some circumstances where research may be performed internationally and/or in settings where there are no IRBs, the UNC-Chapel Hill IRB may, prior to approval of the research, require additional verification and information from people outside the particular research project who are familiar with the customs, practices, or standards of care where the research will be taking place, such as local IRBs or ethics committees, other the UNC-Chapel Hill investigators with knowledge of the region, or a consultant who is an expert on the region. These individuals may either provide a written review of a particular research plan or attend an IRB meeting to provide the UNC-Chapel Hill IRB with recommendations based on his or her expertise.

For Federally funded research, approval of research for foreign institutions or sites “engaged” in research is only permitted if the foreign institution or site holds an Assurance with OHRP and local IRB review and approval is obtained.

Approval of research for foreign institutions or sites “not engaged” in research is only permitted if one or more of the following circumstances exist:

- When the foreign institution or site has an established IRB/IEC, the investigator must obtain approval to conduct the research at the "not engaged" site from the site’s IRB/IEC or provide documentation that the site’s IRB/IEC has determined that approval is not necessary for the investigator to conduct the proposed research at the site.
• When the foreign institution or site does not have an established IRB/IEC, a letter of cooperation must be obtained demonstrating that the appropriate institutional or oversight officials permit the research to be conducted at the performance site.
• IRB approval to conduct research at the foreign institution or site is contingent upon receiving documentation of the performance site’s IRB/IEC determination, or letter of cooperation, as applicable.

1.1 IRB Responsibilities

In addition to standard IRB review, the IRB will consider the following in the review of transnational research:

1. The investigator and research staff are qualified to conduct research in that country including knowledge of relevant laws, regulations, guidance and customs.
2. The consent process and consent documents are appropriate for the languages of the subjects and communication with the subject population. Arrangements are considered to communicate with the subjects throughout the study (e.g., to answer questions).
3. The IRB considers how modifications to the research will be handled. The IRB and investigators should consider as many contingencies (e.g., survey questions) as possible when research is reviewed and approved.
4. The IRB considers how complaints, non-compliance, protocol/research plan deviations and unanticipated problems involving risks to participants or other are handled.
5. The IRB considers how post-approval monitoring will be conducted.
6. The IRB considers if the investigator has obtained the appropriate host country permissions to conduct research (e.g., institutional, governmental or ministerial, IRB, local or tribal). When appropriate, the IRB communicates and coordinates with the local institutions or ethics committees.
7. The IRB considers mechanisms for communicating with the investigators and research staff when they are conducting the research in other countries.

1.2 Investigator Responsibilities

1. It is the responsibility of the UNC-Chapel Hill investigator and the foreign institution or site to assure that the resources and facilities are appropriate for the nature of the research.
2. It is the responsibility of the UNC-Chapel Hill investigator and the foreign institution or site to confirm the qualifications of the investigators and research staff for conducting research in that country(ies).
3. Investigators obtain all appropriate host country permissions to conduct research (e.g., institutional, governmental or ministerial, IRB, local or tribal).
4. It is the responsibility of the UNC-Chapel Hill investigator and the foreign institution or site to ensure that the consent process and consent document are appropriate for the
languages of the subjects and communication with the subject population. Arrangements are considered to communicate with the subjects throughout the study (e.g., to answer questions).

5. It is the responsibility of the UNC-Chapel Hill investigator and the foreign institution or site to ensure that the following activities will occur.

   a. Initial review, continuing review, and review of modification
   b. Post-approval monitoring
   c. Handling of complaints, non-compliance and unanticipated problems involving risk to subjects or others.

6. The IRB will not rely on a local ethics committee that does not have policies and procedures for the activities listed above.

7. Investigators will consider how complaints, non-compliance, protocol/research plan deviations and unanticipated problems involving risks to participants or other are communicated to the IRB.

8. It is the responsibility of the UNC-Chapel Hill investigator and the foreign institution or site to notify the IRB promptly if a change in research activities alters the performance site’s engagement in the research (e.g., performance site “not engaged” begins to obtain consent of research participants, etc.).

9. Investigators cooperate with the IRB regarding how and when post-approval monitoring will be conducted.

10. Investigators consider mechanisms for communicating with the IRB when they are conducting the research in other countries.

1.3 Consent Documents

The informed consent documents must be in a language understandable to the proposed participants. Therefore, the IRB will review the document and a back translation of the exact content contained in the foreign language informed consent document which must be provided by the investigator, with the credentials of the translator detailed in the IRB application or Modification Request form. Verification of the back translation should be placed in the IRB file.

1.4 Monitoring of Approved Transnational Research

The IRB is responsible for the ongoing review of international research conducted under its jurisdiction through the continuing review process in accordance with all applicable federal regulations.

When the IRB and a local ethics committee will both be involved in the review of research, there is a plan for coordination and communication with the local IRB/IECs.

The IRB will require documentation of regular correspondence between the UNC-Chapel Hill investigator and the foreign institution or site and may require verification from sources other than the UNC-Chapel Hill investigator that there have been no substantial changes in the research since its last review.
1 PURPOSE
The UNC IRB has developed this SOP to describe a series of consistent, deliberate steps to mitigate fetal exposure to risk in clinical research studies among women of child-bearing potential (CBP). These procedures are intended for: 1) research studies in which fetal harm from a study intervention is known or can be plausibly inferred, or is unknown; 2) research studies in which the prospect of direct benefit to the woman, the fetus, or both cannot be justified because of fetal risk, and 3) research studies in which the exclusion of pregnant women is scientifically justified. This SOP describes pregnancy-testing requirements for enrollment and continued study participation of women of CBP, as defined below. This SOP does not address requirements for male participants, noting that exposure to interventions in that population may also contribute to adverse outcomes in offspring.

2 PROCEDURE

2.1 Defining “Child-bearing Potential” in Adults
2.1.1 Women are considered of CBP if they (a) are anatomically and physiologically capable of becoming pregnant. Menarche (first menstrual cycle) is the most feasible clinical indicator of the biological potential for pregnancy, thus menstruating females, regardless of age, are considered CBP. Women who have had a hysterectomy or a bilateral oophorectomy are not considered of “CBP”.

2.1.2 A woman is considered past CBP if:
- She is 60 years old or greater, or
- She is age 50 to 59 years and has not menstruated for 12 months or has a follicle stimulating hormone level > 40 mIU/L

2.2 Procedures For Inclusion of Women of CBP in Research
The IRB application and informed consent form should include procedures for inclusion of women of CBP in research. Minimum procedures are outlined below.
2.2.1 For protocols that involve study interventions with *known or suspected* fetal teratogenicity (i.e., thalidomide, vitamin A, ACEi or ARB class of drugs, testosterone and other endocrine disruptors, phenytoin, valproic acid, warfarin, diazepam, chemotherapeutic agents or other anti-cancer agents, radiation, and others), enrolled women of CBP must have a negative pregnancy test (urine or serum) confirmed prior to each study drug administration. Participants should be advised and agree to contraceptive use. Appropriate female contraception is described in section 2.3.1. Participants should also be advised that a negative pregnancy test does not preclude the presence of a very early gestation.

2.2.2 For protocols involving study interventions with *unknown fetal effects*, eligible women of CBP must
1. Have a negative pregnancy test (urine or serum) prior to enrollment
2. Be advised and agree to contraceptive use, which is reaffirmed prior to each study intervention. Appropriate female contraception is described in section 2.3.1
3. Be assessed for likelihood of pregnancy prior to each study drug administration, or monthly at a minimum (i.e., asking and documenting answer to 'Is there a possibility that you could be pregnant?') and also
4. Have a negative pregnancy test (urine or serum) prior to study intervention if investigator deems there is possibility of pregnancy (i.e. participant reports 'yes' to question #3, or reports not using contraception despite sexual activity, or reports missed menstrual period).

2.2.3 For protocols for which there is no anticipated risk for fetal harm but exclude pregnant women solely for scientific reasons (i.e. pregnancy biology may alter or skew results), eligible women of CBP should have pregnancy testing at the discretion of the investigator. Contraception recommendations are also at the discretion of the investigator. Pregnancy testing and contraception recommendations should reflect the protocol’s design regarding discontinuing or withdrawing women if discovered to be pregnant while participating in the study.

2.3 Acceptable methods of birth control for studies that include known teratogens or other interventions that pose a high fetal risk

2.3.1 For protocols that entail the use of known or suspected teratogens or other interventions that pose a high risk to the fetus, women and male participants with female partners, must use reliable and highly effective methods of birth control during the study. Reliable and highly effective methods of female birth control include: two forms of barrier contraception (e.g. condoms and foam; e.g. condoms and diaphragm); long-acting reversible contraception (e.g. subdermal contraceptive implant, intrauterine device, contraceptive injections), and oral contraceptive pills.

2.3.2 Contraceptive measures such as Plan B™, sold for emergency use after unprotected sex, are not acceptable methods for routine use.
2.3.3 Contraceptive requirements may be waived for women who engage in same-sex intercourse or report monogamous heterosexual intercourse with a partner who has had a vasectomy.

2.4 Pregnancy and Minors

2.4.1 North Carolina State law requires healthcare professionals to report abuse and neglect of minors to state and local authorities. A positive pregnancy test in a minor does not, however, indicate abuse or criminal sex act. Hence, researchers do not need to file a report for each positive pregnancy test. The statute leaves it up to the healthcare professional to exercise his/her judgment to assess whether a criminal act has been committed.

2.4.2 Disclosure of a pregnancy to the child's parent should occur when:
- The adolescent agrees to the disclosure or;
- The adolescent is under 12 years of age or younger or;
- The adolescent appears to not understand what is happening or becomes emotionally dysregulated after hearing that they are pregnant (i.e., they do not seem in control of their emotional state or are stating that they are a danger to themselves or others) or;
- The adolescent discloses that they may be in physical danger from their partner or someone else due to the pregnancy.

Disclosure of the minor’s pregnancy to the child's parent in any of the above circumstances should not occur if the adolescent has disclosed unreported or unresolved maltreatment from the parent.

In the rare situation in which the adolescent is not safe to leave the research study for any reason (unreported or unresolved maltreatment in the home where they are currently afraid that they will be seriously injured, suicidal crises with plan, access, and intent, or the situation described here where revealing the pregnancy has precipitated a crisis) the researcher should contact the proper authorities to insure the adolescent's safety (e.g., Orange County mobile crisis unit 1-877-967-8844).

Per North Carolina State law, if a study participant is less than 18 years of age, and the PI or researcher has cause to suspect that the minor participant is dependent, abused or neglected by a parent, guardian, custodian, or caretaker, then the PI or researcher must report the case of the participant to the Director of the Department of Social Services in the county where the child resides or is found.

2.4.3 When pregnancy testing is required, females 10 years and older should be asked if they have started menstruating both in the presence of their parents and privately. Females age 12 or older, or who started menstruating regardless of age, require pregnancy testing if study interventions pose potential for fetal risk.
2.5 Pregnancy testing conducted outside of the UNC Health Care System

2.5.1 Researchers administering urine pregnancy tests at locations outside of the UNC Health Care System (e.g., BRIC, off-campus research facilities) must ensure that the tests are U.S. Food and Drug Administration (FDA) approved and used prior to the date of expiration. Pregnancy tests should only be read by an appropriately trained member of the research team.

2.6 Pregnancy testing and MRI research

2.6.1 The IRB does not require urine pregnancy testing (unless required by the study protocol) for females of CBP who participate in research using FDA-approved Magnetic Resonance Imaging (MRI) machines without contrast unless when asked, they respond that they are or suspect that they are pregnant. Females who verbally state that they are not pregnant do not require pregnancy testing.

2.6.2 Urine pregnancy testing is required within 36 hours prior to all studies using Non FDA-approved MRI machines with or without contrast.

2.7 Pregnancy testing and research using non-FDA-approved coils

2.7.1 A coil is a large inductor with a considerable dimension and a defined wave length, commonly used in configurations for MR imaging. The MRI image quality depends on the signal to noise ratio (SNR) of the acquired signal from the patient. MR imaging coils are necessary to handle the diversity of applications.

2.7.2 Receive-only coils do not introduce any additional energy into the participant and do not change the functioning of the MRI machine. Because no additional energy is introduced, pregnancy testing is not required.

2.7.3 Transmit-Receive coils may introduce additional energy. Because additional energy is introduced, pregnancy testing is required.

2.8 Recommended consent form language:

2.8.1 Parental permission
Pregnancy testing is required for participation in this study; all girls age 12 and older or those older than 10 years who are menstruating, will be tested for pregnancy. Only those testing negative will be allowed to participate. If your child is 12 years and younger, we will share pregnancy test results with you. If you child is 13-17 years of age, we will share pregnancy test results with you if your child 1) agrees that we can share this information with you, 2) is pregnant and does not appear to understand the situation, becomes highly emotional or expresses the potential of harming herself or 3) your child discloses that they may be in potential harm from a partner or someone else due to the pregnancy.

2.8.2 Assent (7-14) and (15-17)
If you are 12 years or older or are 10 years old and have started having your period, pregnancy testing is required for participation in this study. You can only be in the study if you are not pregnant. If you are 12 years or younger, we will tell your parents about your test results. If you are 13 or older, we will tell your parents about your test results if: 1) you agree that we can share this information with them or, 2) you are pregnant and do not appear
to understand the situation, or if you become very emotional or expresses the potential of harming yourself or you feel that are in potential harm from a partner or someone else due to the pregnancy.

2.8.3 Adults (18 years and older)
If you are capable of becoming pregnant, pregnancy testing is required for participation in this study. Only those testing negative will be allow to participate. If you’ve had a hysterectomy (surgical removal of your uterus) or a bilateral oophorectomy (surgical removal of both ovaries), or tubal sterilization (tubes tied or cut), pregnancy testing is not required
1 PURPOSE
To provide guidelines for management of incidental findings in research imaging.

2 PROCEDURES

2.1 Guidelines
There is the inherent risk that incidental findings (IF) may be discovered on research-directed imaging procedures. These IFs may or may not be of clinical significance. The incidence of detected abnormalities when imaging varies depending on a number of factors including age of subjects, health status, the technology used and the expertise of the individual reviewing the image. Potentially significant incidental findings have been reported to occur in 2-10% of imaged subjects. To address these issues, the National Institutes of Health (NINDS, NIDA, NIBIB, NIMH, NIA) and Stanford University co-sponsored a workshop January 2005) that focused on key areas related to brain incidental findings. This UNC policy seeks to implement this group’s recommendations, with special focus on these:

1. In any imaging research, scientists and clinicians should anticipate the potential for Incidental Findings (IFs) in experimental design and establish a process to handle the discovery of an incidental finding.
2. Institutional Review Boards (IRBs) should require that a pathway for managing IFs be fully transparent and should be addressed in the IRB review.
3. The procedure for handling an incidental finding must be made explicit to all participants in the research project in the informed consent.

2.2 Options for Review and Disclosure of Incidental Findings
In the Initial Review Application, the PI should indicate which of the following options is being proposed.
2.2.1 **The PI and IRB feel it is unlikely that clinically significant abnormalities will be present:** (e.g. healthy volunteer subjects with incidence of clinically significant IF similar to health population) then the images do not need to be routinely reviewed by a board certified clinical radiologist credentialed by UNC Health Care.

Many subjects anticipate or expect that if images are obtained, the images would be reviewed for abnormalities, and this may be a form of inducement to participate. It should therefore be made clear to the subject via the consent form and verbal reinforcement that the images will not be formally reviewed by someone qualified to clinically interpret the imaging, and the purpose of their participation in the research study should not be to obtain medical information. Even though there is no routine review of images, in some cases, the PI or technician may become aware of an abnormality that may be of clinical significance. In this case, the PI should consult a board certified clinical radiologist credentialed by UNC Health Care. The subject should not be informed about the possibility of an abnormality immediately after the scan(s) in order to eliminate any risk of creating anxiety prior to review of the scan(s) by a qualified radiologist. The consultation pathway should be outlined in the IRB application and well as how the subject will be notified.

2.2.2 **The PI and IRB feel that the incidence of clinically significant incidental findings is higher than in the general population** (e.g., subjects with known disease(s) that may affect the body part being imaged) then all images should be reviewed by a radiologist credentialed at UNC Health Care or other qualified reviewer. This consultation pathway should be outlined in the IRB application and consent documents.

2.2.3 **If the imaging findings will be used as exclusion criteria or primary study endpoints** then a more detailed review and report of images may be required. In this case a radiologist credentialed at UNC Health Care or other qualified reviewer should be included as an investigator on the study and identified by name.

2.2.4 **If a central reading facility is used, such as in a multisite trial,** the PI should include in the IRB application a description of this process. The IRB application and consent documents should include information regarding whether there will be expert review of images, and should include a description of whether and how the central readers will communicate incidental findings to the PI and subsequently to the subject.

2.3 **Procedures for Review of Imagining and Disclosure**

If images will be read by a qualified reviewer and incidental findings will be reported to subjects, the following procedures should be followed.

2.3.1 Clinically significant results should be reported to subject or legally authorized representative in a timely fashion.

2.3.2 The communication should be made by the qualified reviewer or the PI (if adequately qualified to discuss findings) directly to the research subject, and/or to the subject’s primary care physician (with subject’s permission).

2.3.3 The communication can be oral or in writing with a record kept in the subject’s research file.

2.4 **Informed Consent Process when Research Involves Imaging**
The consent process for research studies involving radiological imaging should address the following issues:

2.4.1 The possibility of incidental findings, and the potential benefits/risks of disclosure of incidental findings.

2.4.2 That research images cannot be assumed to be of clinical quality and, therefore, cannot substitute for a clinical evaluation. Subjects experiencing symptoms for which clinical imaging may be appropriate should be advised to see their primary care physician.

2.4.3 Whether research subjects will be informed of incidental findings. If subjects will be informed of clinically significant findings it should be clear in the consent that the subject agrees to be contacted and informed of the findings. The consent process should inform subjects of the potential risks involved with incidental findings which include anxiety, cost of further clinical evaluation, finding becoming part of their medical record, etc.

2.5 Sample Consent Language

2.5.1 Use when study images will not be routinely reviewed by an expert:

**Possible Discovery of Findings Related to Medical Imaging**

The [MRI, CT, X-ray, etc.] we are using in this research study is not the same quality as a [MRI, CT, X-ray, etc.] that you may have as part of your health care. The images from the [MRI, CT, X-ray, etc.] will not be reviewed by a doctor who normally reads such images (such as a radiologist). As a result, you may not be informed of any unexpected findings. The results of your [MRI, CT, X-ray, etc.] will not be placed in your medical record.

Occasionally the technologist or principal investigator may notice something abnormal on the imaging. If this does occur, the images will be reviewed by a qualified radiologist to determine if there is anything of clinical importance. If something is found to be important then you, and/or your primary care provider will be notified. Any further follow up and costs associated with the incidental finding will be your responsibility. There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are risks as well (such as problems with getting insurance or a job, or feeling worried about a finding for which no treatment is required or appropriate).

For “Healthy Volunteer Studies”, you may include: Do you wish to be informed in case of clinical/relevant unexpected findings? (With yes/no option)

2.5.2 Use when study images will be routinely reviewed by an expert:

**Possible Discovery of Findings Related to Medical research Imaging**

Whenever imaging [MRI, CT, X-ray, etc.] is done, there is the chance of finding something unexpected. Unexpected findings can have clinical significance, or no clinical significance. Clinically significant means that the [MRI, CT, X-ray, etc.] shows a problem that may or require further follow up or treatment. The imaging studies in this study will be reviewed by a qualified radiologist. You will be informed of any findings of clinical significance that may be discovered during the imaging procedure.
There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are risks as well (such as problems with getting insurance or a job, or feeling worried about a finding for which no treatment is required or appropriate). The [MRI, CT, X-ray, etc.] we are using in this research study is not the same quality as a [MRI, CT, X-ray, etc.] that you may have as part of your health care. If you believe you are having symptoms that may require clinical imaging, you should contact your primary care physician.

If the images will be reviewed by a central reader, include the paragraph below:
While your [MRI, CT, X-ray, etc.] will be conducted here at UNC no UNC physician will review the [MRI, CT, X-ray, etc.]. Rather, your images will be reviewed by a “central reader”, a physician designated by the sponsor of this trial to review all of the images. We will inform you of any findings of clinical significance that the central reader tells us about.

3 DEFINITIONS
Incidental Finding: Unexpected imaging finding discovered in the course of conducting a research study that has a potential health or reproductive importance that are beyond the aims of the study and have not been anticipated in the study protocol. Such procedures may include MRI, CT scans, Ultrasound, PET, SPECT, arteriograms, x-rays, fluoroscopy, or other tests that produce an image.

Clinical Significance: Practical importance.
MEMORANDUM

TO: Members of the IRB Committees
FROM: Office of University Counsel
DATE: September 9, 2019
RE: North Carolina Reporting Requirements

INTRODUCTION

A principal investigator (PI) or other researcher may encounter a participant in a research study or clinical trial who the PI or researcher believes may have a condition that is required to be reported to a state-wide official. Generally, if the participant is within a protected category – based on age or mental or physical condition – or if the condition may threaten the public health, then the researcher will have a duty to report to a designated official in North Carolina. The purpose of this memo is to outline the most commonly occurring situations in which a PI or researcher has a duty to report, and clarify to whom the report must be made. Please note that, in addition to making the required external reports described in this memorandum, the PI or other researcher must also report the event to the IRB if the condition or circumstance is reportable as a study-related unanticipated problem involving risks to subjects and others or a study-related adverse event.

REQUIRED REPORTING

1. Dependency, Abuse, or Neglect
   a. Children or Minors

   If a study participant is less than 18 years of age, and the PI or researcher has cause to suspect that the minor participant is dependent, abused or neglected by a parent, guardian, custodian, or caretaker, or that the participant has died as the result of maltreatment from a parent,

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1 “Dependent” is defined as in need of assistance or placement because the child has no parent, guardian, or custodian responsible for the child’s care or supervision or whose parent, guardian, or custodian is unable to provide for the care of supervision and lacks an appropriate alternative child care arrangement. NCGS §7B-101(9).
2 “Abused” has a multi-part definition that includes intentional serious physical injury, creation of a substantial risk of serious physical injury or emotional damage, cruel or grossly inappropriate procedures, criminal sex acts, involuntary servitude or human trafficking, and encouragement or approval of acts of delinquency or moral turpitude. NCGS §7B-101(1).
3 “Neglected” is defined as not receiving proper care, supervision, or discipline; abandoned; not provided necessary medical care or remedial care; living in an environment injurious to the child’s welfare; or placed for care or adoption in violation of law. NCGS §7B-101(15).
4 “Caretaker” is defined as any person other than a parent, guardian, or custodian who has responsibility for the health and welfare of a juvenile in a residential setting. This definition includes stepparent, foster parents, adult members of the juvenile’s household, adult relatives entrusted with the juvenile’s care, house parents or cottage parents in a residential child care facility or residential educational facility, and any employee or volunteer of a division, institution or school operated by the NC DHHS. The definition also includes any person who has the responsibility for the care of a juvenile in a child care facility. NCGS §7B-101(3).

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guardian, custodian, or caretaker, then the PI or researcher must report the case of the participant to the Director of the Department of Social Services in the county where the child resides or is found. **Under the statute, the abuse or neglect must be from a parent, guardian, custodian, or caretaker in order to be reportable.**

The PI or researcher may make the report orally, by telephone, or writing. If the report is made either orally or by telephone, the person making the report must give his/her name, address, and telephone number. The report must include the following items of information as known:

- Name of the child;
- Address of the child;
- Name of the parent, guardian or caretaker;
- Address of the parent, guardian, or caretaker;
- Age of the child;
- Names and ages of other children in the home;
- Present whereabouts of the child if not at the home address;
- Nature and extent of any injury or condition resulting from abuse, neglect, or dependency;
- Any other information which the person making the report believes might be helpful in establishing the need of protective services or court intervention.\(^5\)

Anyone who makes a report as outlined above, who cooperates with the county DSS in a protective services inquiry or investigation, who testifies in any judicial proceeding resulting from a protective services report or investigation, or who otherwise participates in the program authorized by the law is immune from any civil or criminal liability that might otherwise be incurred or imposed for that action, provided that the person was acting in good faith.\(^6\)

### b. Disabled Adults

If a PI or researcher has a study participant who is 18 years of age or older, or who is an emancipated minor, and who is also physically or mentally incapacitated due to:

- mental retardation, cerebral palsy, epilepsy or autism,
- organic brain damage caused by advanced age or other physical degeneration in connection therewith, or
- conditions incurred at any age which are the result of accident, organic brain damage, mental or physical illness, or continued consumption or absorption of substances,

and the PI or researcher has reasonable cause to believe that the disabled adult is in need of protective services due to abuse\(^7\) or neglect\(^8\) by a caretaker, then the PI or researcher must report such information to the Director of the Department of Social Services in the county where the disabled adult resides or is found.

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\(^{5}\) NCGS §7B-301.

\(^{6}\) NCGS §7B-309.

\(^{7}\) “Abuse” is defined as the willful infliction of physical pain, injury, or mental anguish, unreasonable confinement, or the willful deprivation by a caretaker of services which are necessary to maintain mental and physical health. NCGS §108A-101(a).

\(^{8}\) “Neglect” refers to a disabled adult who is either living alone and not able to provide for himself the services which are necessary to maintain his mental or physical health or is not receiving services from his caretaker. A person is not receiving services from his caretaker if, among other things and not by way of limitation, he is a resident of one of the State-owned hospitals for the mentally ill, centers for the mentally retarded or North Carolina Special Care Center he is, in the opinion of the professional staff of that hospital or center, mentally incompetent to give his consent to medical treatment, he has no legal guardian or other guardian, and he needs medical treatment. NCGS §108A-101(m).
The report may be made orally or in writing. The report must include:

- Name of the disabled adult;
- Address of the disabled adult;
- Name of the disabled adult’s caretaker;
- Address of the disabled adult’s caretaker;
- Age of the disabled adult;
- The nature and extent of the disabled adult’s injury or condition resulting from abuse or neglect;
- Other pertinent information.\(^9\)

Anyone who makes a report as outlined above, who testifies in any judicial proceeding resulting from a protective services report or investigation, or who participates in a required evaluation is immune from any civil or criminal liability on account of such report or testimony or participation, unless the person acted in bad faith or with a malicious purpose.\(^10\)

2. Persons with a Communicable Disease

Apart from the general reporting requirements described already in this memo that apply to any person working on a research study or clinical trial, there are particular reporting requirements applicable to principal investigators or researchers who are licensed physicians. Specifically, a physician licensed to practice medicine who has reason to suspect that a person about whom the physician has been consulted professionally has a communicable disease or communicable condition declared by the Commission for Public Health (Commission) to be reported must report information required by the Commission to the local health director of the county or district in which the physician is consulted.\(^11\) Regulations define which diseases and conditions are reportable and specify the time period within which each particular disease must be reported (immediately, 24 hours, or 7 days after the condition is reasonably suspected to exist).\(^12\) For the complete list of reportable diseases and conditions, and their respective reporting timeframes (which is a dynamic list), see 10A NCAC 41A.0101. It is important to note that, by statute, HIV infection is a reportable communicable condition.\(^13\)

While not mandatory, a medical facility in which there is a patient reasonably suspected of having a communicable disease or condition declared by the Commission to be reported, may report information specified by the Commission to the local health director of the county or district in which the facility is located.

PIs and researchers confronted with the foregoing communicable disease reporting requirements must also be mindful of the requirements associated with Certificates of Confidentiality (described further at: [http://grants.nih.gov/grants/policy/coc/cd_policy.htm](http://grants.nih.gov/grants/policy/coc/cd_policy.htm)), noting the NIH Grants Policy options for addressing local reporting requirements in studies for which a Certificate of Confidentiality has been granted.

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\(^9\) NCGS §108A-102(b).

\(^{10}\) NCGS §108A-102(c).

\(^{11}\) NCGS § 130A-135. This mandatory reporting requirement also applies to school principals and operators of child care facilities (child care centers, family child care homes, and any other child care arrangement – although not public schools – that provide child care, regardless of the time of day, wherever operated, and whether or not operated for profit). NCGS § 130A-136.

\(^{12}\) 10A N.C.A.C. 41A .0101. Reportable diseases and conditions can be found online at [http://reports.oah.state.nc.us/ncac/title%2010a%20-%20health%20and%20human%20services/chapter%2041%20-%20epidemiology%20health/subchapter%20a/10a%20ncac%2041a%20.0101.pdf](http://reports.oah.state.nc.us/ncac/title%2010a%20-%20health%20and%20human%20services/chapter%2041%20-%20epidemiology%20health/subchapter%20a/10a%20ncac%2041a%20.0101.pdf)

\(^{13}\) NCGS §130A-135.
3. Injuries caused by suspected criminal violence

Physicians also have an obligation to report injuries caused by suspected criminal violence as soon as practicable to the police authorities in the city where the place of treatment is located.\textsuperscript{14} Although this report is typically made by the healthcare facility where the injury is treated, if a physician treats a patient outside of a hospital or other facility, the physician has an individual duty to report:

- Every case of a bullet wound, gunshot wound, powder burn or any other injury appearing to arise from the discharge of a gun or firearm;
- Every case of illness apparently caused by poisoning;
- Every case of wound or injury caused by a knife or sharp or pointed instrument if it appears to the treating physician that a criminal act was involved;
- Every wound, injury or illness in which there is grave bodily harm or grave illness if it appears to the treating physician that a criminal act was involved; and
- Recurrent illness or serious injury to any child under the age of 18 where the illness or injury appears, in the physician’s judgment, to be the result of non-accidental trauma.

Any physician making such a report in good faith shall have immunity from liability that might otherwise be incurred as the result of making such report.

4. Diagnosis of cancer or benign brain or central nervous system tumor

Health care providers and health care facilities must submit reports to the central cancer registry of each diagnosis of cancer or benign brain or central nervous system tumors in any person who is screened, diagnosed or treated by the provider or facility.\textsuperscript{15} A “provider” includes any person who is licensed or certified to practice a health profession or occupation under the North Carolina laws for Medicine and Allied Health Occupations (including, for example, physicians, dentists, pharmacists, physician assistants, nurses, physical therapists). For purposes of this reporting obligation, “health care facility” is a broad term that expressly includes any facility laboratories or independent pathology laboratories. In the majority of cases, the hospital where a patient is treated typically reports the diagnosis to the central cancer registry. However, laboratories, clinics, and individual professionals that diagnose cancer or benign central nervous system tumors outside a hospital setting are also required to report new cancer cases.\textsuperscript{16} Reports must be made within six months after diagnosis in a format prescribed by the registry.

CONCLUSION

Any researcher working on a research study or clinical trial should ensure that he/she is aware of the statewide reporting requirements as they are applicable to the study. This memo is designed to provide a general overview of some of those requirements\textsuperscript{17} and to emphasize that if a researcher makes a report based upon reasonable cause then he/she will be protected from liability.

\textsuperscript{14} NCGS §90-21.20. If treatment outside city limits, the report is made to the county sheriff.
\textsuperscript{15} NCGS §130A-209. The central cancer registry may be found here: \url{http://www.schs.state.nc.us/units/ccr/}
\textsuperscript{16} See, for example, this letter sent to new physicians: \url{http://www.schs.state.nc.us/units/ccr/documents/New-physician-letter.pdf}
\textsuperscript{17} Please note that this memo does not include all health care professional reporting requirements under North Carolina law. Examples of other reporting requirements not detailed in this memo include certain occupational...
If you have any additional questions, you should feel free to contact any of the following attorneys in the Office of University Counsel:

David Parker, Interim Vice Chancellor & General Counsel  962 1219  david_m_parker@unc.edu
Rebecca Schaefer, Associate University Counsel                962 0338  reschaefer@email.unc.edu

health injuries, NCGS §130A-455; suspicious, unusual or unnatural deaths, NCGS §130A-383; births or fetal deaths occurring outside of a healthcare facility, NCGS §130A-101, 114; health care information that may indicate the existence of a terrorist incident using nuclear, biological or chemical agents, NCGS §130A-476; and death of a migrant worker or worker’s dependent, NCGS §130A-418.
Age of Majority and Exceptions in North Carolina

TO: Office of Human Research Ethics

FROM: Office of University Counsel

DATE: October 11, 2002 (rev. September 28, 2016)

RE: North Carolina Age of Majority and Exceptions

I. INTRODUCTION

Various research studies and clinical trials may involve participants who are minors. The purpose of this memo is to define the age of majority in North Carolina and to provide a general overview of the contexts in which a minor may consent to treatment or participation in research under North Carolina law.¹

II. AGE OF MAJORITY AND INFORMED CONSENT

Under North Carolina law, a minor is “any person who has not reached the age of 18 years.”² Minors are “subject to the supervision and control” of their parents³ and, by definition, do not have the ability to enter into contracts or to consent to medical care for themselves.⁴ Since parents are responsible for their children’s medical care, “they usually have the legal right to control the care – arranging for it, consenting to it or not, 

¹ Federal regulations are beyond the scope of this memo; however, it is important to note that the Department of Health and Human Services has issued regulations protecting human subjects (including children) who participate in the type of research discussed here. The federal regulations are codified at 45 CFR Part 46. Under 45 CFR §46.116(d), the IRB may waive informed consent in certain circumstances. Additionally, 45 CFR §46.408(c) allows the IRB to waive consent for minors when requiring parental or guardian permission is not reasonable given the research protocol (e.g., research involving neglected or abused children).
⁴ Compare N.C. Gen. Stats. Ann. § 7B-3400 (providing that “any juvenile under 18 years of age...shall be subject to the supervision and control of the juvenile’s parents”) with N.C. Gen. Stats. Ann. § 7B-3507 (providing that an emancipated minor has the legal capacity “to make contracts and conveyances, to sue and be sued, and to transact business as if [he or she] were an adult”). In certain emergency situations, North Carolina law does permit a physician to treat an endangered minor without consent from a parent or guardian. See N.C. Gen. Stats. Ann. §§ 7B-3600, 90-21.1. However, a detailed discussion of such treatment is outside the scope of this memorandum. If you have questions about emergency treatment, please contact the Office of University Counsel.

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and paying for it.” It is our understanding that a minor who is a parent has the same rights to control the medical care received by his or her child as a parent who has reached the age of majority.

We are not aware of any North Carolina cases or statutes that specify whether minors can give consent to participate in research. Notably, however, regulations governing research often require investigators to obtain the consent of a minor’s parent(s) or guardian before enrolling the minor in a research study. This requirement applies even if the minor’s parent is a minor. In some cases, therefore, a parent could give consent for his or her child to participate in a research study but could not participate in the same study without permission from his or her parents.

III. EXCEPTIONS

A. Certain Medical Conditions

Under certain, limited circumstances, a minor can give effective consent to receive non-emergency medical care from a physician licensed to practice in North Carolina. More specifically, any minor can consent to receive a licensed physician’s services for the “prevention, diagnosis and treatment of (i) venereal disease and other diseases reportable under N.C. Gen. Stat. § 130A-135, (ii) pregnancy, (iii) abuse of controlled substances or alcohol, and (iv) emotional disturbance.”

B. Emancipation

Emancipation alters the legal status of a minor, rendering the minor an adult for most purposes and relieving his or her parents of their legal rights and duties with respect to him or her. In order to petition for emancipation, a minor must be at least 16

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6 See, e.g., id. at 9-10.
7 As an example, state regulations governing the use of radiation in human subjects research require that the researchers obtain informed consent even if the research is not subject to a federal informed consent requirement. 10A N.C. Admin. Code 15 .0305(b), (c). Also worth noting is a state regulation providing that a minor who resides in a state mental health facility may refuse to participate in any research project even if he or she could not have given his or her consent to participate. 10A N.C. Admin. Code 28A .0306(b). See also, e.g., 45 CFR Part 46.
8 As noted above, consent for emergency medical care is beyond the scope of this memo.
9 N.C. Gen. Stats. Ann. § 7B-3507. An emancipated minor remains subject to laws that impose restrictions based on age, such as laws prohibiting the sale of tobacco products to minors and the sale of alcohol to persons under the age of 21. See Sarah DePasquale, Juvenile Emancipations, ON THE CIVIL SIDE: A UNC SCHOOL OF GOVERNMENT BLOG (December 16, 2015, 11:12 AM), http://civil.sog.unc.edu/ juvenile-emancipations/.
years of age and must have resided in the same county or on federal territory in North Carolina for six months before filing his or her petition with the court. The effect of a final decree of emancipation is that the child “has the same right to make contracts and conveyances, to sue and to be sued, and to transact business as if [he or she] were an adult.”

An emancipated minor “may consent to any medical treatment, dental or health services for himself [or herself].” An emancipated minor also may consent to any medical treatment, dental and health services for his or her child. However, solely becoming a parent is not enough for a minor to establish his or her emancipated status. As noted above, this might create a situation in which an unemancipated minor could give consent for his or her child to participate in a research study but could not participate in the same study without obtaining consent from his or her parent(s) or guardian.

C. Marriage or Military Service

Apart from the formal emancipation process, there are two other methods by which a minor may alter his or her legal status. First, a minor who is legally married will be treated as an adult. Second, a minor who is serving in the armed forces of the United States will be treated as an adult.

We hope that this memo will be useful in your discussions with principal investigators and other researchers on this topic. Please feel free to contact the Office of University Counsel if you have any additional questions.

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15 See, e.g., Health Care for Pregnant Adolescents: A Legal Guide for Healthcare Providers, Anne Dellinger and Arlene M. Davis, UNC-Chapel Hill Institute of Government at 11 (Sept. 14, 2001); cf. N.C. Gen. Stats. Ann. § 7B-3402 (providing that (only) three groups of minors are no longer subject to the supervision and control of their parents: (1) minors who are legally married, (2) minors who serve in the Armed Forces of the United States, and (3) emancipated minors).
# IRB Guidance for Student Research and Class Projects

Federal regulations and university policies require Institutional Review Board (IRB) approval for research with human subjects. This applies whether the research is conducted by faculty or students, by individuals or a group. *Failure to obtain proper approval in advance may jeopardize your data, prevent you from publishing the results, and place you and the university in violation of federal regulations.* At the same time, many class projects are conducted for educational purposes and not as research, and will not require IRB approval. This guidance will help you determine whether you need to get IRB approval before conducting a given activity. Please note that the IRB does not have the option of granting “retroactive” approval after research is done; you should err on the side of submitting or consulting with the IRB if there is any doubt.

## Student Research

Student research activities include, but are not limited to, projects that result in undergraduate honors theses, Masters theses, or doctoral dissertations. *IRB approval is generally required if the intent is to develop new or expanded generalizable knowledge AND human subjects are involved, either directly or through use of identifiable data about them.* Student researchers have the same submission options as any investigator. They may submit as Principal Investigator (PI) with a faculty advisor as co-signator, which may be appropriate for new projects where the student has a leading role. Alternatively, it may be appropriate for the student researcher to be included on an existing project that already has IRB approval, if the student activity is (or will be, after modification) subsumed under that existing study. This latter option precludes the need for a separate IRB application from the student. Each research scenario has its own set of circumstances that will dictate handling. Below are some common scenarios, with likely processing requirements:

<table>
<thead>
<tr>
<th>Research</th>
<th>Human Subjects Research, therefore IRB approval required</th>
<th>Not Human Subjects Research, but if you need documentation from the IRB, submit an IRB application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research that involves <strong>direct interaction</strong> with individuals (e.g., in person, or via mail, email, web survey, or telephone), or <strong>data from human subjects for which the researchers will have access to identifiers.</strong></td>
<td>Submit an IRB application, either with student as PI or listed as study personnel on faculty application; or modify existing study if student project is directly related.</td>
<td>A data use agreement between the researcher and the data custodian may still be required to verify that the researcher will not have access to identifying codes. It is this “de-linking” of data from personal identifiers that allows the IRB to make this determination.</td>
</tr>
<tr>
<td>Research that is limited to <strong>secondary analysis</strong> of data, records or specimens that are either <strong>publicly available, de-identified or otherwise impossible to be linked to personal identities.</strong></td>
<td></td>
<td>If the IRB determines that this project is not human subjects research, human subjects protection training is not required by IRB, but may be required by the faculty advisor.</td>
</tr>
</tbody>
</table>
**CLASS PROJECTS**

Class projects are generally conducted for educational purposes and not as research. While some require submission of an **IRB application** or a determination that IRB approval is not required, many class projects require neither. Instructors and departments are encouraged to contact the relevant IRB for guidance about ways to handle topics such as privacy, confidentiality, informed consent, and professional ethics when class projects are part of the course syllabus. IRB chairs and staff can share expertise related to managing risks of deductive disclosure, coercion-free recruiting, informed consent, and special considerations for projects that include potentially vulnerable individuals. These issues may still remain even when IRB approval is not required, in which case instructors, advisors, departments and schools play an even greater role in providing the appropriate guidance and oversight. Common scenarios:

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<th>Scenario</th>
<th>IRB Action Required</th>
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<tr>
<td><strong>CLASS PROJECTS</strong> involving secondary data analyses that are assigned and conducted as educational exercises, using data that are either publicly available data, de-identified or otherwise impossible to be linked to personal identities.</td>
<td>No IRB action required (neither approval nor determination of human research status)</td>
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<tr>
<td><strong>CLASS PROJECTS</strong> involving secondary data analyses that are assigned and conducted as educational exercises, and that use datasets that include private information and codes that link to identifiers, but the students do not have access to the identifiers.</td>
<td>No IRB action required (neither approval nor determination of human research status)</td>
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<td><strong>CLASS PROJECTS or PRACTICA</strong> that involve direct interaction (e.g., in person, via mail, email, web surveys, or telephone), but where the purpose is training, an educational exercise or professional development, and not research. The project or practicum is not “research” even if students ask people questions as part of learning how to conduct interviews or surveys, take histories, administer assessments, or perform “in-house” evaluations as requested by the practicum site.</td>
<td>No IRB action required (neither approval nor determination of human research status) but may be requested if instructor or students are unsure, or if documentation is required by gatekeepers (e.g., schools, businesses) for access to participants.</td>
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<td>Exception: If a student decides after the completion of a practicum activity to pursue additional activities with the same information for dissemination (e.g., master’s project, conference paper, article), then an IRB application describing research use of secondary data should be submitted for approval, as above.</td>
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<tr>
<td><strong>CLASS PROJECTS or PRACTICA</strong> that involve direct interaction or secondary analyses of private identifiable data and are undertaken as both an educational experience and as research (e.g., results of these activities will be presented publicly or otherwise disseminated, or the data will be stored and used by the students or others as research data).</td>
<td>IRB approval required</td>
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When there are several students in a class doing similar projects, a single IRB application may be submitted by the course instructor as PI, listing all students who will be involved. If projects vary greatly, then it may be preferable to submit individual IRB applications with the student(s) as PI.

The PI must have research ethics certification. Taking into account the sensitivity of the information to be collected, the instructor can require that students complete the CITI online course, or the instructor may provide comparable training, with advance approval of the IRB.
Individual Identifiability of Data

The HIPAA privacy rule sets forth policies to protect all individually identifiable health information that is held or transmitted by a covered entity. These are the 18 HIPAA Identifiers that are considered personally identifiable information. This information can be used to identify, contact, or locate a single person or can be used with other sources to identify a single individual. When personally identifiable information is used in conjunction with one’s physical or mental health or condition, health care, or one’s payment for that health care, it becomes Protected Health Information (PHI).

- Name
- Address (all geographic subdivisions smaller than state, including street address, city county, and zip code)
- All elements (except years) of dates related to an individual (including birthdate, admission date, discharge date, date of death, and exact age if over 89)
- Telephone numbers
- Fax number
- Email address
- Social Security Number
- Medical record number
- Health plan beneficiary number
- Account number
- Certificate or license number
- Any vehicle or other device serial number
- Web URL
- Internet Protocol (IP) Address
- Finger or voice print
- Photographic image - Photographic images are not limited to images of the face.
- Any other characteristic that could uniquely identify the individual

If a communication contains any of these identifiers, or parts of the identifier, such as initials, the data is to be considered “identified”. To be considered “de-identified”, ALL of the 18 HIPAA Identifiers must be removed from the data set. This includes all dates, such as surgery dates, all voice recordings, and all photographic images.
I. Description

Provides accountability, preparation and dispensing clinical trial materials to human subjects

II. Rationale

To comply with the standards set forth by The Joint Commission (TJC) that the pharmacy must control the storage, dispensing, labeling and distribution of investigational agents

III. Policy/Procedure

A. Policy

1. The Investigational Drug Services Pharmacy provides mechanisms for the acquisition, storage, preparation, distribution, and control of clinical trials materials (CTM) for clinical trials with human subjects conducted at the University of North Carolina Healthcare System. These mechanisms are in accordance with the policies and procedures established for the IV Admixture Service, the Ambulatory Care Service, the Central Inpatient Service, and for specific clinical trials and study medications as deemed appropriate by an Investigational Drug Service (IDS) pharmacist.

2. A clinical trial is defined as any experiment that involves the use of a test article and one or more human subjects. An experiment is a procedure done in order to discover or demonstrate some fact or general truth. The use of a Compassionate plea medication at UNC Healthcare shall be considered a clinical trial. However, the following ARE NOT considered to be clinic trials unless a research protocol is being followed:

   a. The use of FDA-approved drug products, biological products, and medical devices for unapproved indications.
   b. The use of extemporaneously prepared formulations of FDA-approved drug products.

3. A test article may be any of the following:

   a. A drug product, approved or unapproved by the FDA.
   b. A biological product, approved or unapproved by the FDA.
   c. A medical device, approved or unapproved by the FDA.

4. Per TJC, the pharmacy must control the storage, dispensing, labeling and distribution of all investigational medications.

5. In emergency situations, approval by the Institutional Review Board may not be a prerequisite for pharmacy services. The attending physician writes a note in the patient’s medical record documenting the emergency nature of the situation. Study medications are dispensed to patients upon the request of an authorized prescriber who has previously...
obtained informed consent from involved patients or patient representative. In emergency situations, dispensing of a test article may not be dependent on obtaining informed consent. However, a “Waiver of Consent” procedure must be followed in accordance with guidelines from the FDA and the Institutional Review Board.

6. Maintain records of the receipt and disposition of study medications in such a way that the Investigational Drug Service can account for the distribution of each unit of medication that it supplies.

7. Investigational agents may be received by the Investigational Drug Services and redistributed to other pharmacy areas of the hospital for preparation and dispensing.

   a. A satellite is defined as a pharmacy area other than the Investigational Drug Services Pharmacy (e.g., Cancer Hospital Inpatient/Infusion Pharmacy [CHIP], Sterile Products Area [SPA]) being responsible for the preparation and dispensing of an investigational agent.

   b. The Investigational Drug Services will be responsible for supplying the pharmacy area with information required to prepare and dispense the agents appropriately.

   c. Inventories of agents may or may not be split between the Investigational Drug Services Pharmacy and the satellite area. This will be dependent upon the protocol.

   d. Investigational Drug Services Pharmacy is ultimately responsible for all investigational agents received.

   e. Satellite dispensing areas must follow all protocol specific drug accountability, preparation and dispensing procedures as outlined in the Protocol Information Sheet for the protocol found in the study notebook.

IV. Original Policy Date and Revisions