



Wake Forest School of Medicine

Human Research Protection Program and Institutional Review Board

Policies and Procedures

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## **I. Authority and Institutional Commitment**

The Vice President for Research Administrations and Operations and the Assistant Dean for Regulatory Affairs and Research Integrity are the authority under which the Wake Forest Human Research Protection Program is established and overseen. These officials have sufficient standing, authority, and independence to ensure implementation and maintenance of the program.

The Wake Forest IRB holds a Federalwide Assurance (FWA00001435), approved by the Office of Human Research Protections (OHRP). This assurance applies to non-exempt research involving human subjects funded by federal agencies subscribing to the Common Rule. Wake Forest University Health Sciences, as an institution involved in biomedical and behavioral research, has in place a set of principles and guidelines that govern the institution, its faculty, staff, IRB members and staff, and the Institutional Official in the discharge of its responsibilities for protecting the rights and welfare of human subjects taking part in research conducted at, or sponsored by the institution. Assurances applicable to federally supported or conducted research must, at a minimum, contain such a statement of principles, which may include an appropriate existing code, declaration, and/or statement of ethical principles as formulated by the institution. The Belmont Report serves as such a document for the Wake Forest University Health Sciences IRB.

The Wake Forest Institutional Review Board has a number of organizations listed as components as part of the assurance. Each component is a wholly-owned subsidiary for which the Wake Forest Institutional Review Board will serve as the IRB of record and researchers will be subject to these policies and procedures.

The mission of the IRB is to protect the safety, rights, and welfare of participants in “human research” defined in applicable federal regulations, with special attention to vulnerable subjects, including but not limited to prisoners, pregnant women, and children. The safety, rights, and welfare of research subjects is the most important consideration and prevails over interests of science and society.

All human research activities and activities of the IRB, regardless of sponsorship, are guided by the ethical principles of The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects Research. The IRB is also guided by the ethical principles for the protection of human research participants as set forth in the Declaration of Helsinki. It operates in accordance with the requirements for human subjects research as set forth in the Code of Federal Regulations at 45 CFR 46 and 212 CFR 50, 56, 312, and 812 and other applicable federal and state regulations and laws, and the ICH-GCP consolidated guidelines, as applicable. Relevant policies and procedures are made available to sponsors, researchers, research staff, research participants, and the Institutional Review Board, as appropriate.

When appropriate, all collaborating institutions and investigators engaged in non-exempt human subjects research, as defined at 45 CFR 46, will operate under an OHRP or other federally approved Assurance for the protection of human subjects.

When any research covered under this policy takes place in a foreign country, the procedures prescribed by the international institution, if any, will afford protections that are least equivalent to those provided in this policy and the research design will consider the local research context where research procedures will occur.

- a. The IRB should obtain necessary information about the local research context through one or more of the following mechanisms:
  - i. Personal knowledge of the local context by an IRB member, through direct experience with the research site, its population, and surrounding community
  - ii. Participation by one or more consultants at convened meetings or through written review. Such consultants should be appropriately qualified with local knowledge of the research context, population, and its surrounding community.
  - iii. Input from an IRB in the country where the research will take place. If an IRB is not available, an appropriate governmental agency may be consulted.
  - iv. Additional information should be supplied to the IRB describing the credentials and training of international collaborators and the plan for reporting events and to preserve the integrity of study data. The IRB must review all research conducted internationally by its faculty and staff. The investigator should also consult with researchers familiar with the culture differences of international research and consider the different customs, habits, and practices of international study subjects with regard to the process of obtaining informed consent.

The IRB functions independently of other institutional entities regarding the protection of human subjects. IRB members may report undue influence to the IRB Director or Institutional Official. Such reports will be evaluated and responded to individually. This authority holds for all institutions designating the Wake Forest School of Medicine IRB as the IRB of record, and for all principal and co-investigators named in research protocols brought before the IRB, regardless of institutional affiliation or location in which the research will be conducted.

The IRB has the authority to take the actions listed below when appropriate.

- a. The IRB has the authority to approve, require modifications in order to secure approval, disapprove, close or suspend any research study based upon its considerations for the protection of human subjects. If the IRB disapproves a research study, it shall provide written notification for its decision and give the investigator an opportunity to respond in person or in writing.
- b. The IRB has the authority to require progress reports from the investigators and oversee the conduct of any research study that is approved. The IRB may request a progress report at any time; however, progress reports will be reviewed at least annually depending on the IRB's assessment of the risk to subjects. The IRB has the authority to have the consent process or any aspect of the research be observed by an IRB member or

a third party whom the IRB determines is qualified and appropriate. The IRB has the authority to obtain all research records and documents associated with an approved study and to audit the conduct of any research study it approves.

- c. The IRB has the authority to suspend, terminate, or modify approval of any study it has originally approved in which an [unanticipated problem](#) involving risk to the safety, rights, or welfare of human subjects or others has occurred. Similar action may be taken in the case of serious or [continuing noncompliance](#) with the requirements of any state or federal regulation or serious or continuing noncompliance with the determinations of the IRB.
- d. Any [suspension](#) or [termination](#) shall be promptly reported in writing to the investigator, appropriate Institutional Official, and as appropriate to OHRP, the study sponsor, the FDA and other appropriate federal departments or agencies. Any report of a suspension or termination shall include the statement of the reason for the IRB's action. The IRB Director or Institutional Official does have the authority to suspend research studies until a convened meeting of the IRB can evaluate the study and issues involved.
- e. The IRB has the authority to place restrictions (including but not limited to length of approval) on any study based upon its considerations for the protection of human subjects.
- f. Additional authority and responsibility may be permitted under institutional policy.

The Vice President for Research Administration and Operations is the Institutional Official. The Institutional Official holds signature authority for all regulatory documents submitted to the Department of Health and Human Services and the Office of Human Research Protections. Signature authority for matters such as Authorization Agreements and Individual Investigator Agreements may be delegated to appropriate parties within the institution. The Institutional Official maintains ultimate responsibility for complaints or concerns about the human research practices.

The IRB Director has been identified as the Human Protections Administrator (HPA) for the institutional FWA, and may serve as an additional point of contact to OHRP officials. All IRB staff, members, and Chairs report to the Director and through the Director to the administration and Institutional Official.

The IRB will report actions and findings to the Institutional Official by making the meeting minutes available upon request. Additional reports, presentations, and issues will be provided upon request.

Proposed research will be evaluated to protect human subjects, but also will be evaluated for scientific validity, either by the IRB or an external entity. When a study is unsponsored, the IRB will serve to provide a scientific and ethical review. IRB members will follow the same guidance as used for National Institute of Health reviewers when conducting a review of scientific validity and will be documented in the reviewer's checklist. Examples of the items under consideration include the use of procedures consistent with sound research design and the whether the design of the study is expected to yield the expected knowledge.

The IRB also serves as the Privacy Board for research and will review protocols to ensure compliance with the HIPAA Privacy Rule, 45 CFR Parts 160 and 164.

## II. Applicability

### 1. Human Subjects Research

Research involving human subjects is governed by federal regulation in order to protect the safety, rights, and welfare of study participants. Research studies that are funded by federal agencies that have agreed to follow the Common Rule are regulated by 45 CFR 46. Research studies that involve FDA regulated drugs or devices are governed by 21 CFR 50 and 21 CFR 56. Studies that are not extramurally funded, and do not involve FDA regulated products are governed by institutional policies.

### 2. Definitions

Research is defined by several agencies. Activities that meet any of these definitions are considered to be research. Listed below are the agency specific definitions for research.

DHHS: Research means a [systematic investigation](#), including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

- i. Systematic Investigation refers to an activity that involves a prospective research plan which incorporates data collection, either quantitative or qualitative, and data analysis to answer a research question.
- ii. Generalizable knowledge refers to information that is produced for the purposes of dissemination to a scientific audience outside of the population served by the covered entity. Some examples include information collected for the purposes of doctoral theses; presentation at a scientific meeting or conference; submission to or publication in a scientific journal; and Internet postings.

FDA: Any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the 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)).

DoD: 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

Belmont Report: an activity designed to test a hypothesis [and] permit conclusions to be drawn

Human Subjects are defined differently by several agencies. Individuals that meet any of these definitions are considered to be the object of the research at WFUHS. Listed below are the agency specific definitions for human subjects.

DHHS: Human subject means a living individual about whom an investigator (whether professional or student) conducting research: (i) Obtains information through [intervention](#) or interaction with the individual, and uses, studies, or analyzes the information; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information.

- iii. Intervention includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
- iv. Interaction includes communication or interpersonal contact between investigator and subject.
- v. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).
- vi. Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

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

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

### **3. Criteria for consideration that a study is not human subjects research**

Certain types of activities may be designated as Not Human Subjects Research (NHSR), and hence are not governed by federal regulations for the protection of human research subjects and do not require review and approval by the IRB. Investigators who believe their research activities involves data about humans, but qualifies as NHSR are strongly advised to seek the advice and counsel of the IRB before engaging in any research activities in order to determine whether the research may be designated NHSR.

A study MAY be considered to be Not Human Subjects Research if:

- 1) It does not meet the federal definition of research (for example, a case report or a quality improvement project). In such cases, investigators are encouraged to consult IRB guidance regarding case reports and quality improvement/assurance projects.
- 2) It does not involve the use of data, information, or biological specimens obtained from human subjects, whether living or deceased (for example, studies using biochemicals, using laboratory animals, or non-human cell lines).

- 3) It involves the use of data, medical records, publicly obtainable information, or specimens obtained from individuals who are no longer living. However in certain circumstances before a determination of NHSR is issued, investigators may be required to furnish the IRB with the methodologies that will be used to assure that the individuals under study are in fact deceased, and may still be subject to the HIPAA and Privacy Rule regulations.
- 4) It involves the use of data that does not contain ANY codes or links to identifiable information. This can be obtained via the safe harbor method (removal of all links, codes, and HIPAA identifiers) or through consultation with a qualified statistician that the identities of subjects are secure and cannot readily be linked to the study data.
- 5) It involves the use of only coded private information or specimens if the following conditions are met
  - a) the private information or specimens were not collected specifically for the currently proposed research project by interaction or intervention with living individuals
  - b) the investigators cannot readily ascertain the identity of the individuals to whom the coded private information or specimens pertain because
    - i) the key to decipher the code is destroyed before the research begins
    - ii) 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
    - iii) IRB-approved written policies and operating procedures for a repository or data management center prohibit the release of the key to the investigators under any circumstances, until individuals are deceased
    - iv) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased

Note that if the investigator(s) at any time obtain the uncoded private information or specimens, or unexpectedly learn the identity of one or more living individuals or believes it is important to determine the identity of one or more of the individuals, the research becomes human subjects research as defined by the federal regulations. If such events occur, the investigator should file a protocol deviation and an amendment. The IRB will then review the protocol under the appropriate review category before further research may be conducted.

#### **4. Determination and notification that a study is not human subjects research**

The IRB Director, IRB Chair, or a qualified designee of the Chair is responsible for determining whether a submission qualifies as NHSR under the federal regulations and guidance provided by OHRP, and may require modifications to the submission prior to making that determination.

Investigators have the ability to conduct projects that do not involve human subjects research without seeking IRB approval, however if there is any doubt as to whether a project qualifies as human subjects research, then they should always err on the side of caution and submit an application to the IRB. If submitted to the IRB, researchers may not initiate a study prior to receiving a memorandum from the IRB declaring it to be NHSR or approved human subjects

research. Each project requires a separate review and determination for NHR. Please note, that if an official determination statement is required from the IRB for publication purposes, this can only be granted prior to initiation of the research project. The IRB should not review projects that have already occurred.

Research conducted on deceased people is still subject to HIPAA privacy laws if PHI is collected as part of the research study. An application must be submitted for IRB review because the IRB serves as the Privacy Board. In order to maintain the confidentiality of the research data, a research study application should be submitted to the IRB to list the data being collected. Research only involving deceased persons will be considered NHR, but protections for PHI must be in place.

If the submission is determined to be NHR, the IRB will send the principal investigator a written or electronic notification which will include: 1) a statement that the IRB has determined the research to be NHR; 2) a statement that the IRB must be informed of any changes to a project, so that it can determine whether the project continues to meet the requirements for NHR. If the submission requires any modification, the investigator is notified of the needed changes. A memorandum with the information listed above is provided only after changes have been made, reviewed, and approved by the IRB Director, IRB Chair, or designee. The convened IRB is informed of all submissions determined to be NHR as information items on future agendas.

If it is determined that a submission does not meet the criteria for NHR, the IRB will notify the principal investigator and the submission will be referred for review through either exempt procedures, expedited procedures, or full board review along with the reviewer's comments and any reviewer recommendation for consideration and final determination.

Projects declared NHR by the IRB must be conducted in the same ethical manner and with the same respect for the privacy and confidentiality of subjects as those studies approved by the Full IRB or by Expedited and Exempt Review.

## III. Records

### 1. Written procedures and guidelines

The IRB will prepare, maintain, follow, and retain written procedures for all of its functions and operations including:

- a. Conducting initial and continuing review of research
- b. Reporting its findings and actions to the investigator and the institution
- c. Determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous review
- d. Ensuring prompt reporting to the IRB of changes in research activity
- e. Ensuring that during the period for which IRB approval has already been given, no change in the approved research may be initiated without prior IRB review and approval, except when necessary to eliminate apparent immediate hazards to the human subjects
- f. Ensuring prompt reporting to the IRB, appropriate Institutional Officials, Sponsor, Office of Human Research Protections, and the Food and Drug Administration, as applicable, of any [unanticipated problems](#) involving risks to human subjects or others, any instances of serious or [continuing noncompliance](#) with these regulations or requirements, relevant determinations made by the IRB, or any suspension or termination of IRB approval for the research.

### 2. IRB membership roster

The IRB shall prepare and maintain a list of IRB members and alternates identified by name, earned degree, representative capacity, indication of experience sufficient to describe each member's chief anticipated contributions to IRB deliberations, and any relationship between each member and the Institution. The IRB membership roster will be provided by the IRB Office to investigators, sponsors, funding agencies, and regulatory agencies as required by regulation or contract.

### 3. Minutes of meetings

The IRB shall prepare and maintain adequate documentation of IRB activities by recording minutes of IRB meetings in sufficient detail to show the following when applicable:

- a. Attendance at the meetings
- b. When an alternate member is a proxy for a primary member

- c. A separate list of any consultants, guests, or others who attended each meeting
- d. Separate deliberations, actions, and votes for each protocol undergoing review by the convened IRB
- e. The basis for requiring changes in or disapproving research
- f. A written summary of the discussion of controverted issues and their resolution
- g. Documentation, including protocol-specific information, justifying:
  - i. A consent procedure which does not include or which alters some or all of the required elements of informed consent
  - ii. Waiving the requirement to obtain informed consent
  - iii. Waiving the requirement to obtain individual [authorization](#)
  - iv. Approving research involving pregnant women, human fetuses, or neonates
  - v. Approving research involving prisoners
  - vi. Approving research involving children
- h. The frequency of continuing review, as appropriate to the degree of risk, and/or time interval for submission of progress reports
- i. When following FDA regulations, the rationale for significant risk/non-significant risk decisions for medical devices
- j. The vote on all IRB actions including the number of members voting for, against, abstaining or recusing for actual or potential conflict of interest. Recused members shall be listed by name and the reason for recusal.
- k. When following DHHS regulations, the justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document.

#### **4. Approval memos**

The IRB shall prepare memos to document the determinations made after reviewing a submissions. Memos are only sent at the time of final approval. Other communication between the IRB staff and study teams, such as comment on the application, alerts for upcoming deadlines, and reminders for outstanding items will be made through the eIRB software system. Approval memos will include the date of approval, pertinent regulatory findings, and will include the printed name of the IRB chair or designee responsible for verifying all criteria for approval have been met. Electronic signatures will not be applied to approval memos.

#### **5. Procedures for reporting actions to the institution**

The IRB shall prepare reports of all new applications approved which will be sent to appropriate institutional representatives. This report will include all pertinent findings and actions of the IRB.

## 6. Retention of documents by the IRB

The IRB shall prepare and maintain adequate documentation of IRB activities for at least 6 years after study closure. All records shall be accessible for inspection and copying by authorized representatives of the federal agencies (OHRP, FDA) or the sponsor at reasonable times and in a reasonable manner. Records are stored in a way that protects confidentiality. IRB records for a protocol are organized to allow a reconstruction of a complete history of IRB actions related to the review and approval of the research protocol. For each protocol reviewed by the IRB, the retained records shall include:

- a. The research proposal reviewed
- b. Any accompanying grant application, investigator brochures or external scientific evaluations
- c. Copies of all correspondence between the IRB and the investigators Recruitment materials
- d. The approved consent documents and if applicable the approved [assent](#) documents
- e. Reports of any [unanticipated problems](#) involving risks to subjects or others, including [adverse events](#) and/or injuries
- f. Records of initial and continuing review
- g. Records of review of additions, revisions and amendments to the protocol and/or consent documents, investigator brochure, etc., and if applicable the [assent](#) documents
- h. Data and safety monitoring reports
- i. Progress reports submitted by investigators and statements of significant new findings provided to subjects
- j. Emergency use reports
- k. Documentation of study closure
- l. Documentation of non-compliance
- m. Scientific evaluations, when these are provided by an entity other than the IRB
- n. For research applications reviewed by expedited procedure, the IRB will maintain records of:
  - o. The justification for using the expedited procedures and the specific permissible category
  - p. Actions taken by the reviewer
  - q. Any findings required by laws, regulations, codes, and guidance
- r. For research applications approved as Exempt, the IRB will maintain records of:
  - s. The justification for exemption determinations
  - t. Actions taken by the reviewer
  - u. Any findings required by laws, regulations, codes, and guidance

- v. For protocols that are withdrawn or closed prior to enrolling a subject, IRB records will be maintained for at least three years after withdrawal/closure.
- w. Budgets, accounting records, and study data are not retained by the IRB. The principal investigator is responsible for retaining documentation pertaining to budgets, accounting records, and study data, and making these records available upon request to the Institutional Official or their designee, or regulatory agencies.

## **7. SOP Revisions**

The IRB maintains standard operating procedures to ensure effective functioning of the human research protection program. The SOPs are available in a searchable format on the IRB website.

## **8. Procedure for Writing Standard Operating Procedures**

The IRB Director, with advice from IRB staff, IRB Chairs, IRB members and/or investigators determines when a new SOP needs to be established. Any staff member may draft an SOP based on his/her specialization. All SOPs are in compliance with federal, state, and institutional regulations. Staff may consult with the IRB Chairs and/or IRB members on IRB related issues in developing the SOPs.

As appropriate, the staff distributes copies of newly drafted SOPs to designated IRB Chairs, IRB members, and/or staff members for review.

If the SOP involves coordination with another University administrative office, the IRB Director, or staff cooperate with the administrative unit involved in drafting the SOP and route the SOP to the appropriate individual representing that office for approval and signature.

The staff ensures that each SOP designates the version date on which it became effective. The most recent revision date indicates that this version is currently in effect.

The IRB Director or designee informs institutional officials of all changes in the SOPs when appropriate.

## **IV. Membership and Operations**

### **1. Membership**

Each IRB shall have at least five members. Additional members may be added to have a sufficient number of members to assure adequate review of the submissions made to the IRB.

The members appointed to the IRB shall be qualified by experience, expertise, and diversity of background to assure the complete and thorough review of submissions commonly made to the IRB. The IRB shall collectively possess the professional competence necessary to review specific research activities and shall be able to ascertain compliance of applications and proposals with institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. If the IRB regularly reviews research that involves a vulnerable category of research subjects, it shall have at least one member knowledgeable about and experienced in working with the category of vulnerable subjects to which the research applies. Examples of categories of vulnerable research subjects include, but are not limited to children, prisoners, and pregnant women.

The IRB shall not consist entirely of members of a single professional group or entirely of officers, employees or persons otherwise associated with the institution, apart from their membership on the IRB. The IRB shall include at least one member whose primary concerns are in nonscientific areas and one member whose primary concerns are in scientific areas. The IRB shall include at least one member who is not associated with Wake Forest Baptist Medical Center and who represents the general perspective of participants. An individual will be considered to have an affiliation with the institutions if they are receiving financial compensation from the institution or otherwise have a financial interest in the institution. If research involves an FDA regulated article, a licensed physician must be included in the quorum. Financial compensation for service on the IRB, if provided, will not be considered to constitute a financial interest in the institutions. The spouse, children, or parents of individuals affiliated with the institutions will also be considered to be affiliated with the institution. Students of the institutions will be considered to be affiliated with the institutions regardless of their financial interest.

Each IRB shall meet the above stated requirements for membership. All IRBs review all types of research. There are no designated specialty review boards. The Dean may constitute additional IRBs that comply with the above membership requirements at his/her discretion. Rosters of the respective boards are reviewed on a periodic basis and updated as needed to ensure appropriate representation.

IRB members affiliated with the institution will be compensated 5% of their salary by the Dean's office for their service on the committee. IRB chairs will be compensated 10% of their salary by the Dean's office for their service on the committee. Non-affiliated members will not be compensated. IRB members are expected to attend at least 60% of scheduled

board meetings. Attendance will be tracked regularly, and members will be informed that if they have not attended 60% of the meetings, they may not be asked to renew their membership on the committee.

IRB members, including non-affiliated members, are covered through the standard liability coverage for its faculty, staff and volunteers.

## **2. IRB Chairperson and Members**

The Dean of the Wake Forest University School of Medicine shall appoint one member to serve as Chair of each board.

The Chair/member shall serve for a term of 3 years and may be reappointed. IRB Chairs and members are responsible for:

- a. Review, approve, require modifications in order to secure approval, restrict, disapprove, terminate, or suspend research studies involving human subjects brought before the IRB
- b. Act as primary reviewer for assigned protocols, provide written comments, and lead discussions of the research study at the convened IRB meeting
- c. Maintain an effective knowledge of subject populations, institutional, and legal requirements and other factors that may contribute to a determination of risks and benefits to subjects and subjects' informed consents
- d. Familiarity with the ethical principles of human research, requirements of federal regulation, applicable state laws, the institution's Federalwide Assurance and institutional policies and procedures for the protection of human subjects
- e. Application of knowledge to ensure the rights, safety and welfare of research subjects
- f. Application of knowledge to ensure compliance with applicable state and federal regulations and laws

Additional Duties of the IRB Chair include:

- a. Reviews and approves Expedited review applications or establishes designee to do so
- b. Mediates resolution of disputes involving human research and IRB actions
- c. Educates IRB members and investigators on the appropriate conduct of human research and IRB policies and procedures
- d. Works with the IRB Director as needed to resolve administrative concerns
- e. Facilitates IRB meetings

The Chair/member serves at the pleasure of the Dean of Wake Forest University School of Medicine and may be removed at any time with written notice.

### **3. IRB Member Conflict of Interest**

Institutional Review Boards (IRBs) hold a position of trust with research subjects, research sponsors, institutions, their professional bodies and society. This position of trust can be put at risk by conflicts of interest that may compromise independence, objectivity or ethical duties of loyalty. To maintain the independence and integrity of ethics review, it is of the highest importance that members of the IRB avoid real or apparent conflicts of interest. To this end, individuals responsible for business development are prohibited from serving as members or ex-officio members on the IRB or carrying out day-to-day operations of the review process. IRB members should identify and address any real or apparent conflicts of interest in order to maintain the public confidence and trust, discharge professional obligations and ensure accountability. IRB members complete an annual Conflict of Interest disclosure which is maintained within the Conflict of Interest office.

If an IRB member has a clear conflict of interest when his/her own research project is under review by the IRB or when he/she have been in direct academic conflict or collaboration with the researcher whose proposal is under review, then that member should recuse from discussion and voting on the research study being reviewed. A conflict of interest also exists when an IRB member has significant financial interest where study outcomes could affect compensation, a proprietary interest in the tested product, a significant equity interest in the sponsor of the study under consideration, or has received significant payments of other sorts from the sponsor of the study under consideration as outlined in this policy.

The IRB Chair will not allow a member to participate in the discussion or vote of any research study in which the member has a potential or actual conflict of interest, except to provide information as requested by the IRB. At the beginning of each meeting, the IRB Chair will remind members to recuse themselves if they have an actual or potential conflict of interest with any submission under review. To manage conflicts of interest, IRB members may recuse themselves from discussion and vote on projects where potential or actual conflict of interest exists, or may apply to the Conflict of Interest Review Committee (CIRC) to determine if a conflict of interest exists and, if so, how it should be managed. IRB members who recuse due to a conflict of interest are not counted towards quorum. IRB members with a conflict of interest are documented in the minutes as being absent with an indication that a conflict of interest was the reason for the absence.

For studies that are reviewed by expedited procedures, [unanticipated problems](#) involving risk to subjects or others, or the review of non-compliance with regulations and local policies, IRB staff members will not assign these reviews to board members with a documented conflict of interest. If an undocumented conflict of interest is discovered, the IRB staff will re-assign the items for review by members without a conflict. If board members are assigned to review items as listed above, it is their responsibility to inform the IRB staff of potential of actual conflicts if not previously documented.

#### **4. Alternate members**

The appointment and function of alternate members is the same as that for regular members.

The alternate member's qualifications are comparable to those of the primary member(s) with whom they substitute. The IRB roster identifies the primary member(s) for whom each alternate member may substitute.

When alternates substitute for a regular member, the alternate member receives the same material that the regular member receives or would have received. The IRB minutes will document when an alternate member replaces a regular member. When an alternate member substitutes for a regular member, the regular member cannot vote.

#### **5. IRB Staff**

The IRB staff consists of the IRB Director, IRB Assistant Director, and five Protocol Analysts. All IRB staff are under the supervision of the Assistant Dean for Regulatory Affairs and Research Integrity and are evaluated on an annual basis. The IRB administrative staff are housed in administrative office space within the Medical Center. Administrative offices are equipped with telephones, computers, printers, copiers, filing systems and other office equipment required to support IRB functions. Computers are connected to the medical center network and the Internet.

IRB staff are also responsible for the set-up of materials needed to conduct board meetings. The medical center will provide the resources required to ensure that the IRB meets regulatory and legal requirements. The IRB meets in various Medical Center conference rooms that are adequate for protocol presentations and to facilitate open discussion.

The Assistant Dean for Regulatory Affairs and Research Integrity conducts a periodic evaluation of the resources available to the IRB staff. Included in this evaluation will be staffing needs, facilities, office space, and other resources necessary for the conduct of the office.

#### **6. Attendance by non-IRB members**

IRB meetings are open to IRB members; whether or not they are in attendance as part of the quorum, IRB staff members, and the Institutional Official as defined at 45 CFR 46.103(c) or their designee. Other individuals affiliated with the medical center may attend IRB meetings as visitors. Any IRB member in attendance may call for a vote requiring a visitor to be excused from the meeting. The decision will be by majority vote.

Visitors do not vote and may not participate in discussion of IRB business unless requested by the IRB. Visitors may not be present for discussion or vote on any research study where they are listed as an investigator, co-investigator or where they have an actual or potential conflict of interest.

## **7. Use of consultants**

The chairman of the respective board, at his/her discretion, may either defer a protocol review to another board with more expertise or invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. The chairman of the respective board is authorized to request review and/or opinions from *ad hoc* consultants concerning any submitted proposal, IRB business or issue presented to the IRB. Such consultants serve at the pleasure of the IRB. The IRB may direct the Chair or other designee to select and appoint the *ad hoc* consultants at their discretion or as defined by the IRB. At minimum, *ad hoc* consultants will be asked to provide a written statement documenting the review and recommendations to the IRB. This written statement will be available for review by all voting board members. *Ad hoc* consultants are not counted towards quorum, and shall not vote on items brought before the IRB.

The IRB is not bound by the opinion, review or findings of *ad hoc* consultants but receives their opinions and reports for information.

## **8. Independent Institutional Review Board**

In situations where the IRB does not maintain the expertise to review protocols submitted to the Board for review and approval, such proposals can be designated to an Independent IRB. An Independent IRB may also be used in situations where there is an Institutional Conflict of Interest which needs to be managed through the review and approval of an IRB other than the medical center IRB. A separate policy is maintained for the designation of an Independent IRB which includes situations where such review may be appropriate.

## **9. Training of IRB Chairs and members**

The IRB Director provides orientation for new members on an annual basis. Each new member receives a packet of IRB reference materials. The IRB Director, in consult with the IRB Chairs and staff, will determine the content of the packet. All IRB members must complete the requirements for education in human subjects research established by WFUHS. New IRB members are also invited to observe a board meeting prior to being listed on the IRB roster.

For research sponsored by the Department of Defense, initial and continuing research ethics education for all personnel who conduct, review, approve, oversee, support, or manage human subject research is required. Education should be appropriate for individual's level of involvement, duties, and responsibilities.

The IRB Director, in consult with the IRB Chairs and staff, will establish means and materials that meet continuing education requirements. The IRB Director periodically provides IRB members copies of articles related to issues relevant to human research from various sources.

## **10. Evaluations**

Board members will be asked to periodically complete an anonymous online survey to evaluate the effectiveness of the IRB Chair as well as IRB staff. Likewise, a survey will be sent to Chairs and IRB staff to evaluate the effectiveness of each board member on the Chair and

Staff member's board. Categories included in the survey may include but are not limited to, timeliness of response, compliance with federal regulations, usefulness of templates and other research material, preparedness for convened meetings, quality of educational opportunities, and meeting conduct. Based on the responses to this survey each member will receive individual feedback, and the IRB staff will focus education topics and training based on the responses and feedback from the evaluation results. Meeting attendance, as well as the timeliness and quality of protocol reviews will be regularly tracked by IRB staff for their assigned board members. This information will also inform the evaluation process and educational needs of board members.

The HRPP will undergo an annual assessment to evaluate compliance with policies and identify areas of poor quality or inefficiency. This assessment will be conducted by the IRB Director with assistance from the Human Research Monitoring and Oversight Specialist, and other designated staff members as needed. One goal of this assessment is to ensure compliance with applicable federal, state, and institutional regulations. This can be done by a review of meeting minutes from each board in order to assess the needs for quorum and the appropriate vote counts and documentation for each agenda item. If areas for improvement are identified, the IRB Director will provide staff and board members with appropriate education on the area(s) in need of improvement, in order to ensure compliance. A second goal of this evaluation will be to monitor the efficiency of the review process. An example of this assessment will be calculating the average number of days from submission to approval of initial applications, amendments, and continuing reviews. A summary of findings and reports will be filed and stored in the HRPP office for future comparison and evaluation of progress. A third goal of the evaluation is to assess the plan and methods for enhancing the understanding of participants, prospective participants, and communities.

## **11. Schedule of Meetings**

The IRB shall meet at regular intervals to discuss submitted proposals in detail and reach a decision on each submission. A schedule of regular IRB meetings is established by the IRB Director in consultation with IRB Chairs, and will be published annually. The date, time, and place of each meeting are provided to members. The IRB Director or any IRB Chair may call the IRB into special session outside the published schedule of meetings. If the IRB is appropriately constituted at such special meetings the IRB may review and act on protocol submissions and conduct any other business.

## **12. Quorum requirements**

A simple majority of the membership listed in the most current version of the IRB's roster on file with OHRP, and is required to convene a meeting and for each vote on a protocol. The quorum must include at least one member whose primary expertise are in nonscientific areas and at least one member whose primary expertise is in scientific areas. If at any time during the meeting a quorum is lost the Board may not vote on material until a quorum is reestablished. The Chair or designee will establish that the requirements for a quorum are met and maintained throughout the meeting. The Protocol Analyst will document in the electronic

IRB system (eIRB) that quorum was obtained and maintained through the meeting. This information will be documented in the minutes of the meeting.

### **13. Technology use in IRB meetings**

A laptop computer will be provided for each IRB member during the meeting in order to facilitate reference to each protocol submission and reviewer checklist during discussion. The electronic submission and IRB record system (eIRB) will be made available to Board members at all times for review of submitted protocols prior to the meeting. The system will be accessible from any device with internet access and the appropriate individual account login and password for member convenience. Teleconferencing or video-conferencing may be used to allow for the attendance of one or more members who cannot physically attend the meetings. When utilizing teleconference or videoconference technology, the members will present the studies assigned to them, discuss concerns and vote on all studies, as they would if they were physically present. Members who will be participating in the meeting remotely will have access to all study materials through eIRB the same as members who attend in person.

### **14. Agenda**

The agenda will be generated by the electronic submission system (eIRB) and will consist of the material submitted and ready for review by the end of business approximately seven days prior to the next Board meeting. All IRB members will have access to the agenda and all submission materials prior to the meeting in order to view material and conduct reviews. In rare instances, exceptions may be made to add a research study to the agenda less than seven days prior to the meeting, when circumstances warrant. The total number of items to be reviewed, including protocols, non-compliance issues, and [unanticipated problems](#), will vary at each meeting. IRB staff will assign studies to members for review. Each agenda will contain a list of submissions reviewed and approved by the expedited process. For the expedited studies, the agenda will contain the study title, the name of the principal investigator, the Primary IRB Reviewer, the date of approval and a link to the study workspace in eIRB, where the full IRB record is stored.

The material provided to members for review will consist of the entire IRB file, via the electronic IRB record system (eIRB). The IRB application will consist of all information necessary to evaluate the study, including but not limited to:

- a. The purpose of the research;
- b. The scientific rationale for conducting the study;
- c. The setting in which the research will be conducted;
- d. Whether prospective participants will be vulnerable to coercion or undue influence;
- e. The inclusion/exclusion criteria;
- f. Participant recruitment and enrollment procedures;
- g. The information contained in any advertisement;
- h. The mode and final version of all advertising;

- i. A description of the procedures being performed already for diagnostic or treatment purposes (standard of care procedures).
- j. The amount and timing of payments to participants;
- k. The risks and potential benefits of participation in the research

## **15. Voting requirements**

Voting may only occur when a properly constituted quorum is established. Members may vote for, against, abstain, or recuse from voting. A member may abstain from any vote without a need to state a reason. Abstaining members continue to count toward a quorum. The minutes will indicate when a member leaves the meeting for reasons other than to recuse and is not present for the vote. The member will not be listed as having voted for, against or abstain. If an investigator, co-investigator or other individual associated with a research study being considered by the IRB is present as a visitor, they must not be present during the discussion and vote for that research study.

A separate vote is taken and recorded for each protocol. Voting is limited to duly appointed IRB members in attendance at a properly convened meeting.

Decisions are based on a majority vote of the members in attendance at a convened meeting. Majority is defined here as greater than 50% of members in attendance. If a majority vote for or in the affirmative, the motion passes or carries; otherwise the motion does not pass or fails. If a motion fails, then the floor is opened for alternative motions to be made. All members in attendance at a convened meeting have full voting rights for all items of business, except if they are required to recuse themselves for actual or potential conflicts of interest. The minutes will list the number voting for, against, abstaining and recusing. Chairs will vote on all protocols for which they do not have a real or perceived conflict of interest. In the case of a tie vote, the IRB may defer to another board.

## **16. Criteria for IRB approval of research**

In order to approve research, the IRB must find that the regulatory criteria for approval established at 45 CFR 46.111(a)(1-7) and when applicable 21 CFR 56.111(a)(1-7).

## **17. Required materials**

All applications submitted for IRB review are screened for complete documentation as well as a preliminary review by IRB office staff. If significant concerns or omissions are noted, then the application is returned to the investigator through the eIRB system. All submissions, no matter the review type are required to submit the following material, when applicable:

- a. completed e-IRB application and submitted by the Principal Investigator
- b. completion of conflict of interest questions by all key personnel
- c. written protocol document
- d. if industry sponsored, then a written protocol document is required
- e. If investigator initiated, then a written protocol is required

- f. consent or [assent](#) document(s) containing compounded HIPAA language when applicable
- g. fact or information sheets
- h. recruitment materials
- i. questionnaires, focus group guides, scripts or other data collection forms
- j. other materials specific to the proposed study (grant application, investigator's brochure, sponsor correspondence with a regulatory agency such as the FDA regarding test item risk)
- k. documentation of review from other committees or institutions
- l. data use agreements
- m. documentation of IRB approval from a study coordinating site
- n. FDA regulatory documentation when an IND or IDE is involved

## **18. Level of review**

The possible review types are described below and correspond to the level of potential risk of harm to the subjects within the proposed research. Each type of review is discussed in more detail in its respective section of this document.

- a. Full board Review
- b. Expedited Review
- c. Exempt Review

The electronic submission system (eIRB) will guide investigators to the appropriate review category based on the level of risk associated with the study protocol. Upon submission, IRB staff and/or board will review the entire application. If the staff or committee does not agree with the level of review selected by the investigator, a different level may be suggested, and the application returned to the investigator for revision.

## **19. Further review/approval of IRB actions**

Research studies approved by the IRB may be subject to further review and approval or disapproval by officials of the institution. These officials may not approve any research study that has been disapproved by the IRB or that has not received full approval by the IRB. No external body, Institutional Official or other individual may approve the conduct of a research study that has not received the full approval of the IRB. The decision of the IRB to disapprove a research study cannot be overturned by an external body, Institutional Official or other individual.

## **20. Appeal of IRB decisions**

To appeal a decision of the IRB, an Investigator must send a written statement with the reasons for appeal to the IRB Chair of the Board which disapproved the study or the IRB Director. This statement will be distributed to all members of the IRB and the research study will be scheduled for reconsideration at a future IRB meeting of a different board. The investigator will be invited to attend this meeting to give a presentation of information

supporting his/her reason for appeal and will respond to any question posed by the IRB. The IRB will discuss and vote on the research study and the investigator's appeal. No further appeal of this decision is then possible. The investigator must not be present for the discussion or vote on their appeal.

Appeals of IRB decisions must be made within 30 days the investigator receiving written notice of the IRB decision. If reconsideration is granted the study would be considered by a neutral IRB within the institution that is free of any potential conflicts of interest.

## V. Full Board Review of Research

### 1. Initial Review

Complete submissions received by the IRB Office are assigned for review at the next available IRB meeting. A submission may be assigned for review by an IRB other than the next available IRB by the IRB Staff, IRB Director or IRB Chair to ensure review by an IRB with appropriate experience and expertise necessary to conduct a thorough review of the research or to facilitate IRB workflow. Submissions may be returned to the principal investigator prior to IRB review if they are determined to be incomplete or contrary to regulations, policies, or procedures. In such case the principal investigator will be informed of the deficiency in the submission.

At least one primary reviewer will be assigned to each submission scheduled for review by the IRB. Additional primary reviewers may be assigned to each item based on complexity of the submission and the need to ensure adequate review. Reviewers will be assigned by the IRB Protocol Analyst responsible for the respective board in consultation with the IRB Director, IRB Chair or designee, as needed, to ensure that protocols are reviewed by board members with appropriate expertise. An IRB Protocol Analyst will also evaluate each protocol and ensure that at least one IRB member knowledgeable about or experienced in working with vulnerable populations will be present at the meeting when research involves such subjects, or has provided commentary for consideration by the board.

Before the scheduled meeting, for each initial submission the primary reviewer(s), and all IRB members including alternates scheduled to attend in place of a regular member, will receive all submitted materials including but not limited to the full protocol, any recruitment materials intended to be heard or seen by the potential subject(s), the proposed informed consent document and if applicable the [assent](#) document, and the investigator's brochure to allow them to make the determinations required by 45 CFR Part 46.111 and 21 CFR Part 56.111. Primary reviewer(s) are encouraged to request additional information from the investigators, prior to the meeting either anonymously through IRB staff or directly if this is needed to complete their review. The primary reviewer(s) will review the proposal prior to the scheduled meeting and will provide written comments and concerns about the submission to the IRB Office. All IRB members are expected to review submissions so that they can individually determine whether the research meets regulatory criteria for approval for new applications, continuing reviews, and amendments.

At the scheduled meeting each protocol will be presented by a primary reviewer in sufficient detail to allow consideration by the full IRB, followed by the comments of any other assigned reviewers. The IRB Chair will present or may designate a member of the IRB or IRB staff to present the protocol if a primary reviewer(s) is not available but has provided their written comments. The written comments of any reviewers not present at the meeting will be available. Following presentation by the primary reviewer(s), the IRB Chair will open the floor for discussion and deliberation by the full IRB. Following discussion and deliberation, the IRB

Chair will ask for a recommendation on the course of action. Any IRB member may put forth a motion.

The IRB may reach one of the following decisions regarding each protocol:

- a. Approval as submitted and the duration of approval.
- b. Provisional Approval: Minor modifications must require only simple attention to and concurrence by the principal investigator. This action authorizes the IRB Chair or designee to grant final approval upon verification that the principal investigator has made the specified modifications.
- c. Postpone: This action defers discussion and action on the application due to the primary reviewers being absent from the meeting and having not submitted their comments.
- d. Table: This action proposes further review by the full IRB pending major revisions to the application, receipt of additional information related to the application, or when substantial issues have been identified that require the response of the principal investigator to IRB concerns. Any time the IRB requests substantive clarifications or modification that may affect the risk determination or any other regulatory criteria for approval of a proposed study; it should be tabled and reviewed again by a convened meeting of the full board. Upon full IRB review of the requested materials or response, a new motion will then be put forth for vote.
- e. Disapproval: This action indicates the IRB believes approval of the protocol is unwarranted.

Resubmission of a previously disapproved protocol requires full IRB review and approval.

The decision of the IRB regarding each submission will be provided to the principal investigator electronically or in writing. If the submission is approved, the principal investigator will be notified of the type of review, the expiration date of IRB approval, that IRB review will be required before any changes are made unless necessary to eliminate any apparent immediate hazard to the subjects, that continuing review is required if the project will continue beyond the approval period and the requirement to report promptly any [unanticipated problems](#) involving risks to subjects to the IRB.

If the submission is approved with minor changes, the principal investigator will be notified of the required changes. A full approval memorandum with the information listed above will be provided only after the minor changes have been made and reviewed and approved by the Chair or designee. If the submission is postponed or tabled, the principal investigator will be notified of the reason. Any response to a postponed or tabled submission must be returned to

a convened IRB for further consideration and action. Tabled submissions are generally returned to the IRB that initially tabled the submission. Submissions which are tabled can be scheduled for review at another board. Submissions that are postponed due to the absence of the primary reviewers are typically scheduled for the next available IRB meeting to reduce any further delays in starting the research project.

If an application is disapproved, the principal investigator will be notified of the reason.

## **2. Continuing Review**

Federal regulations 45 CFR 46.109(e); 21 CFR 56.109(f) require that all research protocols approved by the IRB be subject to continuing review at least every 365 days, or at shorter intervals determined by the IRB, appropriate to the degree of risk. More frequent review is appropriate when the risks to subjects require close monitoring. Factors to consider include:

- a. Nature of risks posed by the research
- b. Degree of uncertainty regarding risks involved
- c. Vulnerability of the subject population
- d. Experience of the investigator
- e. IRB's previous history with the investigator and/or sponsor Projected rate of enrollment
- f. Whether the studies involve novel therapies

The continuing review process must be substantive and meaningful. Review by the convened IRB, with separate deliberations, actions, and votes for each protocol, is required unless the research meets criteria for review through expedited procedures under 45 CFR Part 46.110 and 21 CFR 56.110. At the discretion of the IRB, research activities are subject to audit and verification from sources other than the principal investigator to ensure that no substantive changes have occurred since the last IRB review of the protocol, informed consent document, and other pertinent materials.

### **2.1 Study team procedures for continuing review**

To request continuing review of a protocol, the principal investigator or designee should complete an appropriate request via eIRB. Requests for continuing review of a protocol should be received no less than 30 days prior to the annual renewal date. Requests for continuing review that are submitted to the IRB less than 30 days prior to the annual renewal date are not guaranteed to receive approval before they expire. Requests that are incomplete or lack necessary supporting documentation will be returned without review, and are likewise not guaranteed to receive approval by the date of expiration.

eIRB will automatically send notification to the principal investigator and study team advising of an approaching protocol annual continuing renewal 60 days and 30 days before the approval expiration date. This notification is made as a courtesy only; whether or not the notification ultimately comes to the attention of the principal investigator, it remains his/her

responsibility to maintain a record of the expiration date of IRB approval and submit a timely continued renewal accordingly.

## **2.2 IRB procedures for continuing review**

For continuing review of protocols that are not eligible for expedited review, the IRB staff will designate at least one member of the IRB as the primary reviewer for each protocol. The primary reviewer and all other board members will receive and review a copy of the complete protocol including any modifications previously approved by the IRB and a status report on the progress of the research, including:

- a. The number of subjects accrued
- b. A summary of [unanticipated problems](#) involving risks to subjects or others, withdrawals of subjects from the research, reason for withdrawals, and any complaints about the research that have accrued since the last IRB review
- c. A summary of any relevant recent literature, interim findings, and amendments or modifications to the research since the last review
- d. Any relevant multi-center trial reports including reports from [Data Safety Monitoring Boards](#)
- e. Any other relevant information, especially information about risks associated with the research
- f. A copy of the current informed consent document and if applicable, the newly proposed consent document
- g. A summary of minor deviations occurring over the past year

In conducting the continuing review, the IRB will ensure:

- a. That the required determinations for the approval of research regarding risks, potential benefit, informed consent and safeguards for human subjects continue to be met
- b. The currently approved or proposed consent document is still accurate and complete
- c. That subjects are provided any significant new findings that may relate to their willingness to continue participation [45 CFR Part 46.116(b)(5)].

## **3. Amendments or changes to approved research studies**

Federal regulations state that there should be written procedures for ensuring prompt reporting to the IRB of any changes in research activities, and that changes in approved research may not be initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to human subjects.

IRB review and approval is required before an investigator can implement any changes in an approved research protocol except in the situation described above. This includes, but is not limited to, changes in the informed consent document, protocol document, investigator's brochure (if applicable), advertisements, any other research study-related documents that have been reviewed and approved by the IRB, and any changes in the research team or

environment that affects their ability to safely conduct the study. This policy also applies to any changes in the status of the principal investigator and research team which impact upon conflict of interest issues. Changes in subject recruitment and follow-up status should also be reported to the IRB in the form of an amendment.

It is the principal investigator's responsibility to insure that all changes in an approved protocol, consent form, or other research study related documents are submitted as amendments for IRB review and approval **before they are implemented**. Initiating ANY changes in an active protocol before the amendments has received IRB approval is a violation of both Federal law and institutional policy, and could be considered non-compliance. After receipt of IRB approval, the principal investigator is then responsible for insuring that the most recently- approved version of the informed consent and other study-related documents are used. Approval of an amendment does not reset the expiration date, and a continuing review must still be completed within the appropriate time window.

### **3.1 Procedures to be followed by the study team**

To amend an IRB approved consent form, the research team member must submit an amendment request via eIRB that includes:

- a. A description of the proposed change(s) and the rationale for the change(s)
- b. A copy of the revised documents highlighting the proposed changes. It is recommended that the revised document should include the version number or date in the document footer.
- c. A clean copy of the newly revised documents, including the consent forms for watermarking.

Multiple changes to different parts of the IRB application may be submitted at one time.

Investigators may submit changes in study personnel through a separate Personnel Amendment. However, the Principal Investigator must be changed through an Application Amendment because these types of changes often include changes to the consent forms and/or protocol documents.

### **3.2 IRB procedures for reviewing an amendment request**

Upon receipt of an amendment request, IRB staff will review the submission for completeness; amendments which are incomplete or do not have all required documents will not be considered by the IRB and will be returned without review. Amendment requests may be classified as either minor or major. Amendments that request major or substantive revisions will be assigned for the full board to review.

**Major Revisions** involve changes in procedures which increase the risk to subjects, changes in the protocol which significantly affect the nature or purpose of the study, or changes that are otherwise determined not to meet the criteria for expedited review. Such revisions must be

reviewed by at least one member of the IRB and presented and voted upon at a fully convened IRB meeting. Major revisions include, but are not limited to, changes in the recruitment plan, changes in study eligibility criteria, addition of procedures that have a greater than minimal risk, and revisions to the consent form including the addition of newly identified risks or side effects. Note that changes in inclusion criteria must be approved by the IRB by the amendment process before any subjects may be enrolled who do not meet the inclusion criteria outlined in the currently approved protocol. If an amendment to a protocol previously approved as expedited causes the protocol to no longer qualify for expedited review, the IRB may elect to re-classify the protocol to be reviewed by the full board. If so multiple members could be assigned to review the proposed changes. The IRB also reserves the right to request that the investigator submit a new application if deemed appropriate.

#### **Revisions Implemented Immediately for Safety Reasons**

Amendments that must be made immediately to insure research subject safety are an exception to the requirement for IRB approval prior to implementation. The principal investigator should use his/her judgment when determining if an amendment must be implemented immediately to ensure research subject safety. If this occurs, the IRB Director or IRB Chair must be notified immediately; an amendment request must follow within 24 hours. The request will be considered by the full IRB to determine whether each change was consistent with ensuring the subject's continued welfare.

Following review of the requested amendment, the principal investigator will be notified of IRB approval, any required modifications, clarifications or conditions, or disapproval. If changes to the consent form have been approved, a watermarked copy of the revised consent form will accompany the approval notification. Amendments cannot be implemented without final approval from the IRB.

#### **4. Approval period**

All research studies approved by the full board are subject to continuing review at an interval appropriate to the degree of risk but not to exceed every 12 months. The date of the convened IRB meeting at which the protocol was reviewed and approved either without changes or contingent upon specified changes is the date from which the duration of approval is set. The study will be approved for a maximum of 364 days from the date of initial approval. For example if a study approval date is set on 1/1/2010, then the study will expire if not renewed by 12/31/2010. A memorandum of approval and stamped informed consent form are issued only after all specified changes have been made to the IRB's satisfaction. No part of the protocol can be initiated until full IRB approval is received by the principal investigator. Approval of an amendment does not extend the expiration date established for the study.

## **VI. Expedited Review of Research**

### **1. Initial Review**

The Secretary of HHS has established, and published as a Notice in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The Secretary will evaluate the list at least every 8 years and amend it as appropriate.

Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed at 63 FR 60353-60356 and 63 FR 60364-60367, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110.

An investigator may submit research studies, amendments, and continuing review of approved research studies for expedited review. The same materials are required for review regardless of whether it is ultimately reviewed under the full board or expedited process. The IRB is not required to review research proposals through the expedited review process, even if it appears to qualify under the federal regulations for such review. The decision to review an application through the expedited review process or to refer to the full IRB for review is made by the IRB Director and/or IRB Chairs, or designee. The decision for why a study is not considered for expedited review even though it fits within the Secretary's categories will be documented by the reviewer.

The IRB Chair or their designee is responsible for the expedited review of IRB applications. They may approve the application or require modifications to the application, protocol, consent and accompanying documents prior to approval. A reviewer's checklist will be completed for each application to document the reviewer's comments, concerns, and recommendations. The IRB Chair or their designee may not disapprove submissions through the expedited review process. If a study is not able to be approved by expedited review procedures, the principal investigator is notified and the submission is referred to the full IRB along with the reviewer's comments and recommendations for consideration and final determination. The full IRB is informed of all submissions approved through expedited processes as informational items on the meeting agenda that is distributed via eIRB for each meeting. Each item will have a link to the complete study application from the agenda.

The principal investigator is notified electronically or in writing of the outcome of the expedited review. If the submission is approved, the principal investigator is notified of the type of review, the category within which the study qualifies, the expiration date of IRB approval that IRB review is required before any changes are made unless necessary to eliminate an apparent immediate hazard to the subjects. If the submission requires modification, the principal investigator is notified of the needed changes. A full approval memorandum with the information listed above, along with a stamped informed consent (if

applicable), is provided only after changes have been made, reviewed, and approved by the Chair or designee.

Expedited review procedures may not be used for classified research, or 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.

## **2. Amendments or changes to approved research studies**

Federal regulations state that there should be written procedures for ensuring prompt reporting to the IRB of any changes in research activities, and that changes in approved research may not be initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to human subjects.

IRB review and approval is required before an investigator can implement any changes in an approved research protocol except in the situation described above. This includes, but is not limited to, changes in the informed consent document, protocol document, investigator's brochure (if applicable), advertisements, any other research study-related documents that have been reviewed and approved by the IRB, and any changes in the research team or environment that affects their ability to safely conduct the study. This policy also applies to any changes in the status of the principal investigator and research team which impact upon conflict of interest issues.

It is the principal investigator's responsibility to insure that all changes in an approved protocol, consent form, or other research study related documents are submitted as amendments for IRB review and approval **before they are implemented**. Initiating ANY changes in an active protocol before the amendments has received IRB approval is a violation of both Federal law and institutional policy, and could subject the investigators to serious consequences. After receipt of IRB approval, the principal investigator is then responsible for insuring that the most recently- approved version of the informed consent and other study-related documents are used. Approval of an amendment does not reset the expiration date, and a continuing review must still be completed within the appropriate time window.

### **2.1 Procedures to be followed by the study team**

To amend an IRB approved consent form, the research team member must submit an amendment request via eIRB that includes:

- A description of the proposed change(s) and the rationale for the change(s)

- A copy of the revised documents highlighting the proposed changes. It is recommended that the revised document should include the version number or date in the document footer.
- A clean copy of the newly revised documents, including the consent forms for watermarking.

NOTE: The revised consent form, once approved, is effective only until the ORIGINAL expiration or renewal date of the research study.

Multiple changes to different parts of the IRB application may be submitted at one time.

Investigators may submit changes in study personnel through a separate Personnel Amendment. However, the Principal Investigator must be changed through an Application Amendment because these types of changes often include changes to the consent forms and/or protocol documents.

## **2.2 IRB procedures for reviewing an amendment request**

Upon receipt of an amendment request, IRB staff will review the application for completeness; amendments which are incomplete or do not have all required documents will not be considered by the IRB and will be returned without review.

**Minor revisions** involve changes in procedures that present no more than minimal risk to subjects or do not increase the risks to subjects, and/or revisions that do not constitute a significant alteration of the study design. Minor revisions include, but are not limited to, changes in study team members, corrections of grammatical and typographical errors in the protocol or consent form, changes in telephone numbers, or deletion of survey questions. Minor revisions may qualify for expedited review under 45 CFR 46.110(b)(2). Minor revisions may be reviewed by a designated board member or alternate with appropriate expertise and experience and reported to the full board as information items on the agenda.

The final determination of whether or not an amendment qualifies for expedited review is at the discretion of the IRB Director, the IRB Chair, or designee. All amendments approved by expedited procedures will be presented to a convened IRB as information and included in the minutes. Amendments cannot be disapproved by expedited procedures. Amendments that do not meet the requirements for expedited review, or that for any other reason cannot be approved through expedited procedures, will be presented to the IRB for discussion and vote at a fully convened IRB meeting.

## **3. Continuing Review**

Federal regulations 45 CFR 46.109(e) require that all research protocols approved by the convened IRB be subject to continuing review appropriate to the degree of risk at least every 365 days, or at shorter intervals determined by the IRB, appropriate to the degree of risk.

For studies that are reviewed under FDA regulations, 21 CFR 56.109(f), continuing review is required at least annually, with no exceptions granted for the original type of review, nor the current status of the research.

At the discretion of the IRB, research activities are subject to audit and verification from sources other than the principal investigator to ensure that no substantive changes have occurred since the last IRB review of the protocol, informed consent document, and other pertinent materials.

### **3.1 Procedures to be followed by the study team**

To request continuing review of a protocol, the principal investigator or designee should complete an appropriate request via eIRB. Requests should be received no less than 30 days prior to the annual renewal date. Requests for continuing review that are submitted to the IRB less than 30 days prior to the annual renewal date are not guaranteed to receive approval before they expire. Requests that are incomplete or lack necessary supporting documentation will be returned without review, and are likewise not guaranteed to receive approval by the date of expiration.

Continuing review of research must occur on or before the date of expiration. Failure to submit a complete continuing review application in a timely manner may result in administrative closure of the protocol. Should this occur, then ALL research activity must cease – including recruitment/enrollment of human subjects, continued collection of data or specimens, analysis of data or specimens previously collected, and all interventions or interactions with enrolled human research participants, unless doing so would pose a risk to the participants. Continuation of any research after the expiration date constitutes noncompliance with federal regulations and institutional policy, and could subject the principal investigator and research team to serious sanctions. Additional detailed information regarding study closure can be found in the IRB Study Closure Policy.

eIRB will automatically send notification to the principal investigator and study team advising of an approaching protocol annual continuing renewal 60 days and 30 days before the approval expiration date. This notification is made as a courtesy only; whether or not the notification ultimately comes to the attention of the principal investigator, it remains his/her responsibility to maintain a record of the expiration date of IRB approval and submit a timely continued renewal accordingly.

### **3.2 IRB procedures for continuing review**

For continuing review through expedited review procedures, the IRB Chair or designated IRB member(s) will receive and review all of the above-referenced documentation for continuing review of research studies, including the complete protocol. Following review of these materials the Chair or designee may reach one of the following decisions:

- Approval as submitted and the duration of approval.
- Approval with minor modifications and the duration of approval. Minor modifications must require only simple attention to and concurrence by the principal investigator. This action authorizes the Chair or designee to grant final approval upon verification that the principal investigator has made the specified modifications.
- Refer to the full IRB for consideration

## VII. Exempt Research

Federal regulations identify certain categories of research activities involving human subjects that may qualify for exemption from the federal regulations for the protection of human research subjects.

The federal regulations outlined in 21 CFR Part 50 and 21 CFR Part 56 which cover research under FDA oversight, do not allow for the IRB to designate research as exempt.

The investigator should complete an eIRB application with the information requested through the electronic submission system to obtain an exemption determination. If it is determined that a submission does not meet the criteria for exempt status, the IRB will notify the principal investigator and the submission will be referred for review through either expedited procedures or by the full board review along with the reviewer's comments and any reviewer recommendation for consideration and final determination.

Investigators do NOT have the authority to make an independent determination that research involving human subjects is exempt, and may not initiate a research study prior to receiving a memorandum from the IRB approving its exempt status. Each project requires a separate review and approval for exemption.

If the submission is determined to be exempt, the IRB will send the principal investigator a written or electronic notification which will include: 1) the date of IRB approval; 2) the exempt category(s) under which the research has been classified; 3) a statement that the principal investigator must report promptly any [unanticipated problems](#) to the IRB. If the submission requires modification prior to final determination, the principal investigator is notified of the needed changes.

The full board is informed of all submissions determined to be exempt by listing them on the meeting agenda and providing an electronic link to all study specific documents.

Categories of Research may be exempt through the provisions of 45 CFR 46.101(b) (1)-(6).

### 1. Application of the Subparts

As defined in the federal regulations the subparts (B-D) may not all be applied uniformly. Subpart B has no restrictions; therefore any exempt category could be applied to studies involving pregnant women. Subpart C is not permitted to utilize exempt review. Therefore, studies that involve prisoners are not permitted to be approved under any exempt criteria. Subpart D may be applied to exempt category 1, 3, 4, 5, and 6. Studies that involve children are not permitted under exempt category 2.

### 2. Other considerations

The IRB does require a status report every three years for research studies declared exempt.

Revisions or modifications to exempt studies must be submitted and approved by the IRB prior to implementation.

Research studies declared Exempt by the IRB must be conducted in the same ethical manner and with the same respect for the privacy and confidentiality of research subjects as those studies approved by the full IRB or by Expedited Review. If there are interactions with participants, a consent process may be appropriate. At minimum the consent process should disclose the following information:

- The activity is research
- A description of the procedures
- That participation is voluntary
- Name and contact information for the Researcher

## VIII. Study Closure, Suspension, or Termination

### 1. Regulatory Background

#### Suspension or Termination

The convened IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB approval, that has been associated with serious or [continuing noncompliance](#), or that has been associated with harm to the rights and welfare of human subjects. Any suspension or termination of approval shall include a statement of the reason for the IRB action.

The IRB Chair or designee has the authority to request that the IRB suspend approval, however the final decision on whether to suspend or terminate a study must come from a convened meeting of the full board with established quorum. This request may be made when the continuation of the research may adversely affect the rights and welfare of research subjects or when the IRB needs additional information to ensure that the rights and welfare of subjects are protected and there is insufficient time to have the convened IRB review the situation.

The IRB reports the suspension or termination promptly to the investigator and appropriate institutional official(s). If the research is funded by an extramural agency, federal regulations dictate whether the funding agency must be informed that IRB approval has been suspended or terminated. Principal investigators (PIs) are responsible for informing the funding agency of any suspension or termination of funded research.

Reporting to federal regulatory agencies is not required if the PI voluntarily closes down a study to new subject accrual or temporarily halts the research procedures. The IRB, IRB Chair, IRB Director, or administrative officials may recommend voluntary closure to the PI, but the PI makes the decision whether closure is appropriate. However, if the IRB, IRB Director or IRB Chair requires suspension or termination, then the incident is reportable.

#### **Closure**

Per 1998 FDA Information Sheet, investigators are required to report to the IRB when a study is closed. Once a study has reached the point where follow-up of human subjects AND data analysis is complete, the principal investigator may choose to close the study.

However, the principal investigator and study team continue to have the responsibility for maintaining the privacy and confidentiality of data related to the study.

### 2. Procedures to be followed by the study team

#### Suspension or Termination

The PI is responsible for notifying enrolled subjects of any suspended or terminated research protocol. The PI should consider the appropriate procedures for withdrawal of enrolled subjects, taking into account their safety, rights, and welfare.

### **Closure**

To close or end IRB approval of a completed study, the principal investigator should provide a final status report to the IRB that includes:

- The number of subjects accrued
- A summary of [adverse events](#) and any [unanticipated problems](#) involving risks to subjects or others, any withdrawal of subjects from the research, or complaints about the research that have accrued since the last IRB review
- A summary of any relevant recent literature, interim findings, and amendments or modifications to the research since the last review
- Any relevant multi-center trial reports, including reports from chartered DSMBs
- Any other relevant information, especially information about risks associated with the research
- A copy of the current informed consent document

## **3. IRB procedures for closing a research study**

### **[Suspension](#) of IRB Approval**

A request or motion to suspend an approved protocol may be made by the IRB Chair or Director, however the convened IRB determines and documents in the minutes the reasons for suspending the research and any information needed from the PI and/or corrective actions or events that need to take place for the IRB to consider a withdrawal of the suspension.

When a suspension involves the withdrawal of current subjects from a research protocol, the IRB considers alternatives that protect subjects currently enrolled to ensure that harm is not incurred from such withdrawal. Such considerations may include, but are not limited to, possible transfer of subjects to another investigator, arrangement of clinical care outside the research, continuation of some research activities under the supervision of an independent monitor, permitting follow-up of subjects for safety reasons, or requiring reporting of [adverse events](#) or outcomes to the IRB and the sponsor. If the PI leaves the institution, and a new PI is not named at the time of departure, the IRB may suspend study activities until a new, appropriately qualified PI is approved.

If the IRB suspends approval, the IRB Chair or Director documents the reason for suspension and notifies the PI in writing. Correspondence with the PI may include, but is not limited to, the following:

- An explanation of the extent of the suspension in terms of enrollment, recruitment, interventions, interactions, and data analysis;

- The reasons for the suspension, an explanation of the reasons for the decision, and an offer to the investigator to respond to the convened IRB in writing;
- A request for a description of any procedures needed to protect the rights and welfare of current subjects if the suspension involves currently enrolled subjects;
- A description of whether follow-up of subjects for safety reasons is permitted or required.

### **Termination of IRB Approval**

The convened IRB determines and documents in the minutes the reasons for terminating the research.

When a [termination](#) involves the withdrawal of current subjects from a research protocol, the IRB considers alternatives that protect subjects currently enrolled to ensure that harm is not incurred from such withdrawal. Such considerations may include, but are not limited to, possible transfer of subjects to another investigator, arrangement of clinical care outside the research, continuation of some research activities under the supervision of an independent monitor, permitting follow-up of subjects for safety reasons, or requiring reporting of [adverse events](#) or outcomes to the IRB and the sponsor.

IRB staff will notify the PI of the termination in writing. The notification may include, but is not limited to, the following:

- An explanation of the extent of the termination in terms of enrollment, recruitment, interventions, interactions, and data analysis;
- The reasons for the termination, an explanation of the reasons for the decision, and an offer to the investigator to respond to the convened IRB in writing;
- A request for a description of any procedures that need to be followed to protect the rights and welfare of current subjects if the termination involves currently enrolled subjects;
- A description of whether follow-up of subjects for safety reasons is permitted or required; An explanation that any request for appeal of the termination must be made within 30 days from date of the notification.

The IRB determines which institutional officials to notify of the suspension and whether to report the suspension to an external agency. (See Reporting to External Agencies SOP) Copies of suspension correspondence may also be sent to other administrative units in accordance that are relevant. These groups could include, but are not limited to, the Radiation Safety Committee, Cancer Review Committee, Clinical Research Unit, Biosafety Committee, or the Office of Sponsored Programs.

### **Closure**

Upon receipt and review of these materials, the IRB Office will provide the principal investigator with acknowledgement of the study closure, and will finalize the study closure in eIRB. All study closures are reported to a convened IRB as information.

#### **4. Renewal of activity in a closed state**

Once a study has been closed, for any reason, the principal investigator must submit a new protocol application to the IRB for review and approval should he/she wish to renew ANY research activity related to the study- including any [intervention](#) or interaction with previously recruited subjects; accessing, analyzing, or transmitting any data which has been stored as part of the study; or review of subjects' clinical records for research purposes.

## IX. Informed Consent

### 4. 1. Regulatory Background

Informed consent is a requirement of non-exempt human subjects research. Informed consent is a document as well as a process, both of which are equally important. Obtaining consent is an ongoing process between the investigator (or designee) and prospective subjects whereby information is exchanged and the subject is given the opportunity to ask questions. In most cases, federal regulations require informed consent and documentation of the consent process. In certain circumstances, however, a waiver may be granted.

Unless signed informed consent is waived or not required by the IRB or federal regulations, investigators may not conduct research involving human subjects unless legally effective informed consent of the subject or the subjects' [legally authorized](#) representative has been obtained. Informed consent is legally effective if it is both obtained from the subject or the subject's legally authorized representative and documented in a manner that is consistent with applicable laws of the jurisdiction in which the research is conducted. Wake Forest School of Medicine institutional policy requires a participant to personally sign, date, and notate the time a consent form is signed.

An investigator shall seek such consent only under circumstances that provide the prospective subject or the legally authorized representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

The information that is given to the subject or legally authorized representative shall be in language understandable to the subject or legally authorized representative. Subjects or legally authorized representatives whose primary language is not English should be consented and provided with a copy of the consent form in their native language.

No informed consent may include any exculpatory language, through which the subject or representative is made to waive or appear to waive any of the subjects' legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence. Exculpatory statements include statements in which a subject is asked to agree to or accept something that is unfavorable to the subject.

The informed consent requirements in this policy are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed in order for informed consent to be legally effective. In addition, nothing in this policy 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.

The signature of a LAR may be used in research studies where the subject is incompetent or otherwise unable to provide informed consent (e.g., unconscious). The IRB considers the ethical principles outlined in the Belmont Reports when considering whether or not a research

study is allowed to obtain the consent of the LAR. When the IRB approves consent by an LAR, a signature line and date must be included in the signature section of the informed consent document. A description of the LARs relationship to the subject must also be included.

The issue as to who can be an LAR is determined by the laws of the jurisdiction in which the research is conducted (e.g., local or state law). North Carolina has such law that addresses consent by someone other than the subject for participation in research. The IRB relies on the Medical Center policy for obtaining informed consent for treatment, surgical operations and procedures (PPB-BRD-04) which states the order of an LAR. The IRB identifies who can be an LARs in the following order:

It is the responsibility of the research team to assess the LAR status prior to enrolling a subject in a research trial which has been approved by the IRB. The status (the relationship to the subject) must be documented on the informed consent form. The use of an LAR to consent on behalf of a potential research subject must be outlined in the IRB application and approval must be granted by the IRB.

In situations where the research participant could not sign the informed consent document due to unconsciousness or similar state, and whose LAR signed the informed consent document on their behalf, the research participant should be informed of the research study at the earliest possible time. The research subject should be consented to continue their participation in the research study or given the opportunity to stop their participation.

The foregoing applies to studies in North Carolina. For studies that will be conducted in other states or countries, the investigator will be expected to determine local requirements for [legally authorized](#) representatives, minors, and [guardians](#) in consultation with the University Legal Counsel.

## **2. Required Elements**

The basic elements of informed consent (as stated in 45 CFR 46.116 and 21 CFR 50.25) must be provided to each participant unless the IRB has approved an alteration of the basic elements. When following FDA requirements, there is a statement that a description of the clinical trial will be available on <http://www.clinicaltrials.gov> as required by U.S. law. The website will not include information that can identify the participant. At most the website will include a summary of the results. The participant can reach the website at any time.

## **3. Documentation of Informed Consent**

The documentation of informed consent as outlined below is required unless the IRB has specifically waived the requirement under applicable federal regulations.

Informed consent shall be documented by the use of a written informed consent document. The informed consent document must be signed and dated by the subject or the subject's [legally authorized representative](#). If a subject's legally authorized representative consents on

their behalf, a statement of the relationship of the LAR to the subject must be outlined. The version of the informed consent most recently approved by the IRB must be used. A copy of the signed informed consent shall be given to the person signing the document.

#### **4. 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:

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

Studies that follow FDA regulations and guidance may be eligible for a waiver of documentation of the consent process only under circumstances that meet criteria number 2 above.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research. This written statement must be reviewed by the IRB prior to being provided to participants.

#### **5. Use of the Short Form Written Consent Document**

The IRB also allows for the use of a short form written consent document. A short form is a summary of the research being performed and would not embody all of the required elements of an informed consent document. A short form states that the elements of informed consent required by federal regulations have been presented orally to the subject or the subject's [legally authorized representative](#). A short form may be used as a substitute if potential subjects are blind, illiterate, non-English speaking, or have other conditions preventing them from obtaining legally effective consent. When this method is used all the following conditions must be met:

- There shall be a witness to the oral presentation
- For participants who do not speak English, the witness should be conversant in both English and the language of the participant.
- The IRB shall approve a written copy of what is to be said to the subject or the representative.

- The short form itself is to be signed and dated by the subject or the legally authorized representative.
- The witness shall sign and personally date both the short form and a written copy of what was said to the subject or the representative. The witness's signature attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject of the subject's LAR, and that informed consent was freely given by the subject or the subject's LAR.
- The person actually obtaining consent shall sign a written copy of what was said to the subject or the representative
- A written copy of what was said to the subject or the representative shall be given to the subject or the representative, in addition to a copy of the short form

## **6. Waiver of Informed Consent or the Elements of Informed Consent**

The IRB may approve a consent process which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that the research is not subject to FDA regulations and meets the required conditions stated in 45 CFR 46(c) or 45 CFR 116(d).

If a waiver of consent is granted by the IRB, this will be communicated to the investigator in their approval memo, and also a record will be maintained in the electronic study file.

## **7. Additional Signatures**

The Common Rule as outlined in 45 CFR 46 does not require a witness signature, or the signature of the principal investigator, when the research subject signs a standard informed consent document which embodies all of the required elements. Federal regulations require the signature of the subject or the subject's [legally authorized representative](#) (LAR) and the date on which the subject or their LAR sign the informed consent document.

## **8. Re-consenting Research Subjects**

The federal regulations do not specifically address the re-consenting of subjects; however, they do require that research subjects be provided with any significant new findings developed during the course of the research which may relate to the subjects willingness to continue participation. While not specifically addressed in the regulations, the Belmont Report provides an additional ethical requirement to provide research subjects with significant new findings that might affect their long-term health even after they have completed participation in a research study. Neither the federal regulations nor the Belmont Report provide guidance on the type or extent of documentation required to satisfy these regulatory or ethical responsibilities.

The IRB requires that research subjects be re-consented to participate in research studies when changes to the research protocol affect the safety, rights and welfare of the subjects or the subjects' willingness to continue participation in the study. For example, amendments filed with the IRB related to research related risks, would require re-consenting of the research subjects. When filing an amendment, investigators should outline their plans for re-consenting subjects when changes to the protocol and consent would affect the safety, rights and welfare of research subjects.

Minor changes to the informed consent document including but not limited to typographical errors, would not require the re-consenting of research subjects.

## **9. Data retention when participants withdraw from a clinical trial**

Investigators should give participants a variety of options with regard to the management and confidentiality of study data once a participant withdraws from a trial.

When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remains part of the study database and may not be removed. The consent document cannot give the participant the option of having data removed. Investigators should either include options of withdrawal in the initial consent document, or have a separate document, that has been approved by the IRB prior to use, that describes the following options for data integrity following withdrawal.

A researcher may ask a participant who is withdrawing whether the participant 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 participant would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the participant's information.

The researcher must obtain the participant's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). The IRB must approve the addendum consent document.

If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the researcher must not access for purposes related to the study the participant's medical record or other confidential records requiring the participant's consent. However, a researcher may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.

## **10. 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.

### **11. Obtaining Consent Remotely**

In some cases, investigators may not be able to have face to face contact with potential study participants, LARs, or parents granting permission to participate in research. In such cases, the investigator may still obtain consent remotely. In order to obtain legally effective consent, the investigator or member of the study team should provide two copies of the approved consent form to the participant/LAR/parent. After received, the investigator should speak with the participant/LAR/parent, presenting the elements of consent, the content of the study, and answer any questions. At the end of the discussion, the investigators should advise the participant/LAR/parent to sign and date one form and return it. The second form should be kept by the participant/LAR/parent for documentation. Upon receipt of the signed form, the investigator should sign and date with the current date, and add a note detailing the date discrepancy. No study procedures will begin until the IRB approved method of obtaining consent is completed.

### **3. 12. Adults Unable to Consent**

When investigators are likely to approach adults who lack the ability to consent, the IRB evaluates the following:

- The proposed plan for assessment of the capacity to consent is adequate.
- [Assent](#) of the subjects is a requirement, and if so, whether the plan for [assent](#) is adequate.

Examples of research subjects who are adults and unable to [assent](#) are the decisionally impaired and mentally handicapped.

When adult subjects are unable to consent, a legally authorized representative may consent on their behalf. The criteria for who may qualify as an LAR are determined by state law. The listing of approved classes of individuals that may serve as an LAR is included in section 16.3 of this document.

#### **4. 13. Monitoring the consent process**

The IRB has the authority to observe and monitor the consent process as a method to protect subjects. The IRB may consider monitoring the consent process in the following circumstances:

- An investigator has had previous non-compliance cases for failure to obtain consent in accordance with the regulations.
- The research will involve subjects who are cognitively impaired or unable to consent.
- An investigator is conducting his or her first research project.

The IRB may observe the consent process in person with the study team and subject present, or may review consent records and source documentation to ensure the methods used to obtain consent were appropriate.

#### **14. Compensation for Research Injury in Informed Consent**

As required by 45 CFR 46.116, an explanation of compensation in the case of research related injury is required in studies of greater than minimal risk. For studies that are sponsored by non-profit or federal entities, Wake Forest has established an insurance policy which is included in the consent form. For studies that are sponsored by for-profit entities, it is important that the description of compensation and liability in the informed consent document be consistent with the terms agreed to in the Clinical Trials Agreement between the institution and the sponsor. Therefore, the IRB may approve either the template language established by the institution or the following statement, if the terms of the contract have not been negotiated at the time of review:

**Injury language will be provided following completion of negotiation and approval by Sponsor and WFUHS.**

If the above statement is employed by an investigator, it will be noted in their approval letter that subjects should not be enrolled in the study until an amendment has been submitted, verified with the contract, and approved by the IRB.

**Please Note:** If a subject is injured as a result of participation in a research study, Wake Forest School of Medicine does not allow for coverage by the sponsor contingent upon first billing of the subject's insurance. For example, accepting payment for any costs to treat a study related injury that the subject's insurance does not cover is not permitted. Sponsors are expected to provide the same level of injury liability coverage to all subjects regardless of their ability to pay treatment costs through other means.

## X. HIPAA

The Health Insurance Portability and Accountability Act of 1996 (HIPAA), Public Law 104-191, was enacted on August 21, 1996. One requirement of the Act was to establish privacy regulations governing individually identifiable health information. These regulations, known as the Privacy Rule (45 CFR parts 160 and 164), became effective April 14, 2003.

The Privacy Rule establishes minimum Federal standards for protecting the privacy of individually identifiable health information. The Privacy Rule confers certain rights on individuals, including:

- Right to receive a written notice about the entity's privacy practices
- Right to inspect and have copied one's own medical record
- Right to amend the record, where appropriate
- Right to request confidential communications regarding health information
- Right to request that uses and disclosures be restricted
- Right to obtain an accounting of all non-routine disclosures
- Right to complain about privacy violations to the entity and to the Department of Health and Human Services

The Privacy Rule governs the use and disclosure of "protected health information." Information about the payment for health care also may be PHI. To qualify as PHI, the information must identify the person directly or be sufficiently specific that the person could be identified. The Privacy Rule governs all PHI in all forms, whether electronic, paper, medical media, or conversation.

Under the Privacy Rule, PHI may be used only for treatment, payment or operational activities unless individual [authorization](#) is granted or the use is specifically allowed by law. Apart from treatment activities, providers must use only the "minimum necessary" information to accomplish the intended purpose. Exceptions to the minimum necessary standard include uses and disclosures related to treatment, disclosures to the individual patient, and certain disclosures required by law.

Wake Forest University Health Sciences and the North Carolina Baptist Hospital are covered entities and are subject to the regulations outlined in the HIPAA Privacy Rule.

The HIPAA Privacy Rule outlines the conditions under which Protected Health Information may be used and disclosed for research purposes. The research provisions of the Privacy Rule apply to both covered entities that may disclose individually identifiable health information that they created or maintain, and to researchers who, as members of a covered entity, may either receive individually identifiable health information from covered entities or who may create individually identifiable health information as part of research activities.

## 1. Using Protected Health Information for Research

Any research use of PHI is limited to the following conditions:

Permission is granted by the patient, through a written [authorization](#) form

**OR**

One of the following criteria is met:

- a) The information is completely [de-identified](#) and no longer governed by the HIPAA Privacy Rule
- b) A waiver of the individual [authorization](#) requirement is obtained from an institutional review board (IRB)
- c) The information is compiled into a “[limited data set](#)” and a [data use agreement](#) is executed for the disclosure of protected health information outside the institution
- d) The activity qualifies as “preparatory to research”

## 2. Retention of Protected Health Information

Research subjects may revoke their research [authorization](#) at any time during the research study. If permission is revoked, the Privacy Rule allows continued use and disclosure of the information that was obtained prior to the revocation, to preserve the integrity of the study. For example, the researcher may use the information to account for study withdrawals, to report [adverse events](#) to FDA, or to comply with study audits. Once [authorization](#) is revoked, the subject is withdrawn from the study and no additional information can be collected on this subject by the investigator. The revocation of an [authorization](#) should be submitted to the principal investigator of the research study. Upon receipt of such revocation, the investigator should submit a copy to the WFUBMC Privacy Office.

### Written [Authorization](#)

Written authorization from the research subject is the default requirement for use of protected health information in research. Prospective research, such as a clinical trial, generally requires prior authorization. The authorization differs from informed consent in that the authorization obtains specific permission to use and disclose protected health information for the research project and focuses on privacy risks and states how, why, and to whom the PHI will be used and/or disclosed for research purposes. An Authorization must contain the following specific core elements and required statements.

### De-identification

Certain research projects can be accomplished through the use of [de-identified](#) data. The Privacy Rule provides two methods to de-identify data. Under the first method, all of the 18 elements specified in the Privacy Rule as identifiers are removed.

The second way is to have a qualified statistician determine, using generally accepted statistical and scientific principles and methods, that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by the anticipated recipient to identify the subject of the information. The qualified statistician must document the methods and results of the analysis that justify such a determination. This documentation must be kept for at least 6 years from the date of its creation or the date when it was last in effect, whichever is later.

### **3. Waiver of Individual [Authorization](#)**

For some types of research, it is impracticable for researchers to obtain written Authorization from research participants. To address these situations, the Privacy Rule allows the IRB to approve a waiver or an alteration of the Authorization requirement in whole or in part for the research uses and [disclosures](#) of PHI. A complete waiver occurs when the IRB 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 determines that an Authorization is not required for all PHI uses and disclosures for research purposes, such as disclosing PHI for research recruitment purposes. The IRB may also approve a request that removes some PHI, but not all, or alters the requirements for an Authorization (an alteration) such as screening information.

In order to approve a waiver or an alteration of the Authorization requirements the IRB must document that the regulatory criteria under 45 CFR 164 are satisfied.

In planning a project that employs a waiver of authorization, researchers should consider their responsibility to comply with the minimum necessary standard of the Privacy Rule. Only the minimum amount of protected health information should be used and disclosed, as necessary to accomplish the goals of the research. For example, date of birth should not be recorded if age will suffice.

The Privacy Rule requires that when PHI is accessed through a waiver of authorization, the researcher's access must be included in the patient's accounting of disclosures. For example, accessing PHI in a patient's medical record under a waiver of authorization requires an accounting of the disclosure. (see Accounting for Disclosures, below).

Waiver of authorization for research studies that qualify for review through Expedited Procedures may be carried out by the IRB Chair or one or more IRB members designated by the Chair, otherwise the waiver of authorization must be made by the full convened IRB.

### **4. [Limited Data Set](#)**

When only certain identifiers are needed it may be possible for a researcher to use a limited data set. A limited data set is considered to be PHI under the Privacy Rule.

Prior to disclosing the limited data set, the researcher must provide a Data Use Agreement. You must retain a copy of the Data Use Agreement with the study documents and provide the recipient of the limited data set with a copy.

The data use agreement must contain the elements required under 45 CFR 164.

## **5. Receiving a [Limited Data Set](#) from outside the institution**

When receiving a limited data set from an entity outside WFUBMC, the researcher must request a [Data Use Agreement](#). If a covered entity is the recipient of a limited data set and does not have a data use agreement in place, the covered entity has violated the Privacy Rule.

While the Privacy Rule dictates the identifiers that *must* be removed in a limited data set, the minimum necessary standard of the regulation remains in effect for any other health information. Researchers are responsible for requesting only the information that is necessary to accomplish the research purpose. For example, if age expressed in years, months, or days will suffice, date of birth should not be requested.

## **6. Preparatory to Research**

The Privacy Rule allows researchers to review PHI in medical records or elsewhere to prepare a research protocol, or for similar purposes preparatory to research. This review allows the researcher to determine, for example, whether a sufficient number or type of records exists to conduct the research. Importantly, the covered entity does not permit the researcher to remove any PHI from the covered entity. This includes data obtained within the covered entity being placed on a lap top computer that can be carried outside the covered entity if that lap top or other device is personally owned by the researcher. If the lap top or portable device is owned by the institution, it can be taken off campus and still be part of the covered entity. This means that researchers may review PHI as preparatory to research but may not record any PHI unless it meets the waiver requirements.

The Privacy Rule requires that when PHI such as a medical record is accessed for activities preparatory to research, the researcher's access must be included in the patient's accounting of disclosures (see Accounting for Disclosures, below).

## **7. Research Recruitment under HIPAA**

The requirements of the Privacy Rule impact the way in which potential subjects are identified and recruited for studies. According to the rule, health care providers involved in the treatment of an individual are allowed to talk with their patient about enrolling in a research study. This discussion would not require an [authorization](#).

However, if the health care provider shares the patient's information with a researcher who is not involved in the patient's care, some form of privacy permission must be in place, either through written authorization from the patient or a waiver of authorization for the

recruitment activity. The written permission or the waiver allows the researcher to view the patient's protected health information in order to make a determination about study eligibility.

Investigators can identify potential subjects for their research through the preparatory to research provision. However, if the researcher wishes to contact that individual, a waiver of authorization must be granted by the Institutional Review Board.

Once a potential subject has been identified, research teams should follow appropriate ethical standards about contacting the patient. Preferably, the initial contact should come from someone who is known to the patient as having legitimate knowledge of their health status, based on an established clinical relationship.

## **8. Allowable Recruitment Practices**

1. Health care providers who are conducting a study may talk with their own patients about the option of study enrollment.
2. Health care providers may use their own knowledge of the patient's condition and their knowledge about a colleague's study to inform their patients about a study. At that point, two possibilities exist:
  - a. The provider gives the researcher's contact information to the patient, and the patient initiates the contact.
  - b. The patient signs an [authorization](#) so that the provider can give the patient's name to the researcher.
3. Health care providers may release their patient records to a researcher, if the researcher obtains a waiver of authorization from the IRB. Then the researcher can review the chart, determine eligibility, and work with the provider on contacting potential subjects.
4. The researcher posts IRB-approved flyers or advertisements, and eligible patients directly contact the researcher.

## **9. Research on Decedents**

Research on decedents is not subject to human subject regulations; however, it is subject to the HIPAA Privacy Rule. In order to access PHI, such as medical records, on decedents, the researcher must provide the holder of the PHI with assurances that:

- The information being sought is solely for research on decedents
- The information being sought is necessary for research purposes

The holder of the PHI has a right to require documentation of the death of the individuals. HIPAA regulations require that when a medical record is accessed for research on decedents, the researcher's access must be included in the patient's accounting of disclosures (see Accounting for Disclosures, below).

## **10. The IRB's Role Related to the Privacy Rule**

The Privacy Rule establishes the authority of the IRB 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.

When acting upon a request to waive or alter the Authorization requirement, the IRB will follow the procedural requirements, including using either the normal review procedures (review by the convened IRB) or the expedited review procedures.

For research studies that qualify for review through Expedited Procedures under the procedural requirements, a request to approve a waiver or alteration of the Authorization requirements may be carried out by the IRB Chair or one or more IRB members designated by the Chair. The IRB will advise all its members of such requests for waivers or alterations of the Authorization requirement by including the approval of the waiver in the IRB records. If the head of the Federal department or agency (or his/her designee) regulating the research has restricted, suspended, terminated, or chosen not to authorize an institution or IRB to use expedited review procedures, the IRB cannot grant waivers or alterations of the Authorization requirement on an expedited basis.

Following approval of a request to waive or alter the Authorization requirements the IRB will provide the investigator documentation of the approval that 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 (see Waivers or Alterations of the Authorization Requirements)
- A statement that the waiver or alteration was reviewed and approved under established review procedures

Under the Privacy Rule, an Authorization may be combined with the informed consent document for research. If the informed consent document is combined with an Authorization meeting the Privacy Rule's requirements, 45 CFR part 46 and/or 21 CFR parts 50 and 56 require IRB review of the combined document.

Effective January 1, 2005, the institution is requiring that all HIPAA Authorization language be combined in the informed consent form for all new studies and those undergoing continuing review.

## **11. Other Research Related Topics**

### **Research Databases and Repositories**

The creation of a research database or repository, and the use or [disclosure](#) of PHI from a database or repository for research purposes, may each be considered a research activity under the Privacy Rule. When using existing databases and repositories, it may be impractical to obtain written authorization to use the PHI. In this case, the IRB can waive the requirement for written authorization if the established criteria are met.

The Privacy Rule specifies three ways in which protected health information can be compiled for a research database or repository:

- Individual, written authorization is obtained from the subject of the information
- Waiver of the individual authorization requirement is obtained from an IRB or privacy board
- The PHI is obtained from a covered entity in a limited data set and accompanied by a [data use agreement](#)

Prospective collection of data or tissue samples for a research repository requires IRB approval and will generally also require informed consent and a privacy authorization. Researchers should note that if approval is granted for the general purpose of constructing and maintaining the repository, then subsequent studies of the material also will require IRB review. Depending on the nature of the subsequent study, the IRB will determine whether consent/privacy authorization is required or if the consent/privacy authorization requirement is waived.

## **12. Minimum Necessary Provision and Role-Based Access**

When conducting research apart from an individual privacy authorization, HIPAA requires that researchers request and maintain only the minimum necessary protected health information to accomplish the research purpose. The holder of the medical record may reasonably rely on the researcher's representation that the information being requested is indeed the minimum necessary. The HIPAA principle of role-based access complements the standard of minimum necessary. Researchers are responsible for designating personnel who need access to study files that contain identifiable data. Access should be commensurate with the role on the research project.

## **13. Accounting for Research Disclosures**

Federal regulations allow an individual the right to receive an accounting of [disclosures](#) of protected health information made by a covered entity in the six years prior to the date on which the accounting is requested. The accounting process was established so that they could learn about how their information was disclosed in cases where written permission was not required. Disclosures of PHI from an individual, such as from their medical record, that are made under a waiver of authorization, for activities preparatory to research, or for studies on decedents must be included in the accounting process. The holder of the PHI is responsible for having a process that meets the accounting for disclosure provisions in the Privacy Rule. The

Principal Investigator in the research study is responsible for assisting the holder of the PHI in fulfilling their accounting duties and is therefore required to account for such disclosures.

An example of when researchers must account for disclosures is when performing a retrospective chart review. This type of research typically includes a waiver of authorization to access and use PHI. Researchers must account for such disclosures.

The accounting for each disclosure must include the following:

- The date of the disclosure.
- The name of the entity or person who received the protected health information and, if known, the address of such entity or person.
- A brief description of the protected health information disclosed.
- A brief statement of the purpose of the disclosure that reasonably informs the individual of the basis for the disclosure or, in lieu of such statement, a copy of a written request for a disclosure.
- An accounting of disclosures should be kept on file by the Principal Investigator for a minimum of six years.

#### **14. Additional Uses and Disclosures of Protected Health Information**

A covered entity can use and disclose PHI without an authorization under the following circumstances: To the extent that the use or disclosure is required by law. For example, a covered entity may disclose, without authorization, information to a cancer registry if the disclosure is required by law.

Disclosure of PHI to a public health entity that is authorized by law to collect or receive information for purposes of preventing or controlling disease, injury, or disability. For example, a covered entity can report, without written authorization, information regarding an individual's HIV or Hepatitis status.

Information can be disclosed to the FDA when the information involves an FDA-regulated product or activity. For example, while participating on a clinical trial where the FDA has jurisdiction, serious or unexpected [adverse events](#) can be reported without written authorization.

Disclosure of PHI to oversight agencies, such as the Office of Human Research Protections (OHRP) for activities authorized by law that are necessary for the oversight of government-related programs is allowed without written authorization.

#### **16. Certificates of Confidentiality**

Investigators working with vulnerable populations or collecting sensitive information may obtain a certificate of confidentiality to protect the study participants. A certificate of confidentiality protects participants from compelled disclosure of identifying information about subjects enrolled in sensitive biomedical, behavioral, clinical or other research.

Certificates of Confidentiality are issued by the National Institutes of Health (NIH) and other HHS agencies to protect identifiable research information from forced or compelled disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in civil, criminal, administrative, legislative, or other proceedings, whether federal, state, or local. Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects, such as damage to their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help to minimize risks to subjects by adding an additional level of protection for maintaining confidentiality of private information. IRB approval of the research is required prior to obtaining a Certificate of Confidentiality.

Effective October 1, 2017, all NIH funded studies will be issued a certificate of confidentiality.

## XI. FDA Regulated products

### 1. **Investigational Drug**

Research involving use of an investigational drug requires an Investigational New Drug (IND) from the Food and Drug Administration (FDA) unless the study is exempt from the requirements for an IND by meeting all of the conditions stated in 21 CFR 312.2(b).

The IRB Chair (or designee) will determine if a study involving an investigational drug meets the exemption criteria as defined in 21 CFR 312.2 (b). If the exemption criteria are not met, the IRB Chair (or designee) will inform the PI, in writing, that a formal IND determination by the FDA is required and provide a rationale for this decision. The PI will be required to contact the FDA to either obtain an IND or written documentation that an IND is not necessary before any further review by the IRB will occur.

It is the investigator's and sponsor's responsibility to maintain appropriate storage and handling of investigational drugs. The protocol analyst and board reviewers assigned to the protocol will assess the plan to control the investigational drugs so that they are used only in approved research protocols and under the direction of approved investigators.

Studies involving an investigational drug will undergo initial and continuing review at a convened meeting unless the study meets the criteria for review by expedited procedure.

### 2. **Investigational [Medical Device](#)**

Research involving the evaluation of the safety or effectiveness of a device requires an Investigational Device Exemption (IDE) from the FDA, unless:

- a. The study is exempt from the requirements for an IDE by meeting all of the conditions stated in one of the seven categories in 21 CFR 812.2(c); **or**
- b. The device under study is determined to be a [non-significant risk device](#) and the abbreviated IDE requirements as defined in 21 CFR 812.2(b) are met.

The IRB Chair (or designee) will determine if a study involving an investigational device meets the exemption criteria as defined in 21 CFR 812 (c). If the exemption criteria are not met one of the following will occur:

- a. The study will be scheduled for review by the fully convened IRB to determine if the device is a [non-significant risk device](#) as outlined under the abbreviated IDE requirements in 21 CFR 812(b); or
- b. The PI will be informed by the IRB Chair (or designee), in writing, that a formal IDE determination by the FDA is required and provide a rationale for this decision. The PI will be required to contact the FDA to either obtain an IDE or written documentation that an IDE is not necessary before any further review by the IRB will occur.

It is the investigator's and sponsor's responsibility to maintain appropriate storage and handling of investigational devices. The protocol analyst and board reviewers assigned to the protocol will

assess the plan to control the investigational devices so that they are used only in approved research protocols and under the direction of approved investigators. Studies involving an investigational device will undergo initial and continuing review at a convened meeting unless the study meets the criteria for review by expedited procedure.

### **3. Device Risk Determination**

The Investigational Device Exemption (IDE) regulations (21 CFR 812) describe two types of device studies: significant risk (SR) and [non-significant risk devices](#) (NSR).

Studies involving the proposed use of a [medical device](#) will be reviewed by the full convened IRB. The IRB will determine if the proposed use of the investigational device does or does not meet the regulatory definition of a [significant risk device](#). This determination will be made separate and in addition to the research risk determination.

For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB is required. In addition, informed consent must be obtained for either type of study [21 CFR Part 50].

### **4. Humanitarian Use Devices (HUD)**

An **HUD** is a device that is intended for the diagnosis or treatment of a disease or condition that affects fewer than 4,000 individuals in the United States per year.

FDA regulations provide for the submission of a humanitarian device exemption (HDE) application, which is similar in both form and content to a pre-market approval (PMA) application. However, unlike a PMA application, an HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The HDE application must, however, contain sufficient information for the FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, 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. Additionally, the HDE applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that the device could not otherwise be brought to market unless it is granted HUD status.

HDE regulation do not require informed consent because an HDE provides for marketing approval, and so use of the HUD does not constitute research or an investigation which would normally require informed consent. Since there is nothing in the law or regulation that preempts a state or institution from requiring prospective informed consent, the IRB requires that either informed consent be obtained or a description of what information will be provided

to the patient and a statement that the use of the HUD will be noted in the patient's medical record or on clinical procedure consent be provided.

The unlabeled or off-labeled use of a HUD is not permitted under the HDE regulations. The use of a HUD is limited to the indication specified in its product labeling. Use of a HUD for an indication that is NOT specified in the respective product labeling must comply with the FDA's and IRB's provisions for the [Emergency Use](#) of Unapproved Medical Devices or be through a separate IDE protocol that has been approved by the FDA and IRB.

Applications for approval of use of an HUD are made through eIRB process.

The IRB is responsible for initial and annual continuing review of the HUD. For initial review of a protocol HUD, the FDA requires a full board review. However, the FDA allows expedited review procedures for continuing review, since the initial review is always by the full board and use of a HUD within its approved labeling does not constitute research, unless the IRB determines that full board review should be performed.

## **5. Expanded Access to Investigational Test Articles**

[Investigational products](#) are sometimes used for treatment of conditions either for a single subject or for a group of subjects who are not eligible for participation in on-going clinical trials but who do not meet the requirements for [Emergency Use](#) of an Investigational Drug or Biologic.

The procedures that have evolved for an investigational new drug (IND) used for these purposes reflect the recognition by the Food and Drug Administration (FDA) that, when no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects or the thoroughness and scientific integrity of product development and marketing approval.

The IRB, along with the FDA, allow for the use of an HUD for compassionate use.

A physician who wishes to use a HDE-approved device for compassionate use should provide the HDE holder with:

1. A description of the patient's condition and
2. The circumstances necessitating use of the device,

3. A discussion of why alternative therapies or diagnostics are unsatisfactory

4. Information to address the patient protection measures.

If a physician undertakes a compassionate use, he or she should devise a schedule for monitoring the patient, taking into consideration the specific needs of the patient and the limited information available regarding the risks and benefits of the device for this unapproved use.

FDA guidance updated in October 2017 permits an IRB to waive the requirement that single-patient expanded access requests must be reviewed by the convened IRB. Therefore, it would be permissible for an IRB chair or designee to grant approval for the request before treatment begins without being considered by the convened IRB. Approval of the HUD is reported to in the IRB minutes along with all other research studies submitted to the Board for approval.

## **6. Billing Compliance Issues**

Notification of approval from Clinical Trials Office is required in addition to IRB approval before a device can be used. It is the responsibility of the investigator to coordinate billing issues with the departments referenced above. If subjects will incur costs as a result of the use of the device, this should be clearly outlined in the informed consent document.

Wake Forest School of Medicine does not allow payments for research procedures to be covered by the sponsor contingent on the subject's inability to pay through other means (i.e. we do not allow sponsors to make payment for research procedures to be made available only to subjects who are under or uninsured or otherwise unable to cover the costs themselves or in cases where such costs are billed to a study subject's insurance and paid only by a study sponsor only in the event of an insurance denial. All subjects must receive the same level of cost coverage for research procedures.

Approval from Compliance Manager and WFUP Director of Regulatory & Reimbursement Services is required in addition to IRB approval before a HUD can be used. It is the responsibility of the investigator to coordinate billing issues with the departments referenced above. If subjects will incur costs as a result of the use of the device, this should be clearly outlined in the informed consent document.

## **XII. Emergency Use of a test article in Life Threatening Situations**

Federal regulations recognize that, in a life threatening situation where standard treatment is unavailable and treatment with an [investigational product](#) or procedure is thought to be in the best interest of the subject, the ability to obtain full Institutional Review Board (IRB) approval may not be possible.

The IRB may agree that a situation represents an emergency exemption for the use of an unapproved drug, device, or procedure without full IRB approval in accordance with Food and Drug Administration (FDA) and Department of Health and Human Services regulatory standards.

FDA regulations contain a specific provision for this exemption from IRB review. HHS regulations do not contain such provision but contain a section 46.116(f) that specifies that nothing in the HHS regulations is intended to limit the authority of a physician to provide emergency care to the extent the physician is permitted to do so under applicable federal, state and local law.

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

The emergency use provision in the FDA regulations is an exemption from prior review and approval by the IRB. **The exemption, which may not be used unless all of the conditions described in 21 CFR 56.102(d) exist, allows for one emergency use of a test article without prospective IRB review.** FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. FDA acknowledges, however, 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.

When an unapproved device may offer possible life saving alternative treatment, but an IDE for the device does not exist, or the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE, the device may be used in an emergency setting.

IRB policy recommends that the IRB be notified prior to use of an investigational drug in an emergency situation; however, this is not required. Investigators should submit a written notification to the IRB Director or Executive Chairmen to confirm that the use of the investigational product complies with FDA regulations. In addition, this notification should not be construed as IRB approval. Notification is used by the IRB to initiate tracking to ensure that the investigator files a report within the five day time-frame required by 21 CFR 56.104(c). The FDA regulations do not provide for expedited IRB approval in emergency situations. Therefore,

"interim," "compassionate," "temporary" or other terms for an expedited approval process are not authorized.

## 1. Requirements for Emergency Exemption from Prospective IRB Approval

The FDA permits researchers to use an [investigational product](#) in an emergency situation without prospective IRB approval, provided that all the following criteria are met:

- The subject is confronted with a life-threatening situation necessitating the use of the test article.
- 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.
- There is not sufficient time to obtain IRB approval.
- There is not sufficient time to obtain informed consent
- When using a medical device, there is no time to obtain an IDE number through the FDA. The FDA and IRB expect the investigator to determine whether these criteria have been met to assess the potential for benefits from the unapproved device, and to have substantial reason to believe the benefits will exist. The investigator may not conclude that an emergency exists in advance of the time when treatment may be needed based solely on the expectation that IND or IDE approval procedures may require more time than is available.

In the event that a device is to be used in the circumstances meeting the criteria listed about, the device developer should notify the Center for Devices and Radiological Health (CDRH), Program Operation Staff by telephone (301-594-1190) immediately after the shipment is made. Nights and weekends, contact the Division of Emergency and Epidemiological Operations (202 857-8400).

Note: an unapproved drug or device may not be shipped in anticipation of an emergency.

## 2. Informed Consent Considerations

Even for an [emergency use](#), the investigator is required to obtain informed consent of the subject or the subject's [legally authorized representative](#) unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

- 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 from the subject's legal representative.
- d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If the investigator is not able to obtain informed consent prior to using an investigational device due to circumstances meeting the criteria stated above, the investigator should inform the subject of the investigational procedures at the first available opportunity, and provide documentation of the information provided to the subject/LAR to the IRB.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article.

### **3. Emergency Use IND**

The need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in the usual manner. In such cases, the FDA may authorize shipment of the drug for a specified use, usually conditioned upon the sponsor filing an appropriate application as soon as practicable. Requests for such authorization may be made by telephone or other rapid communication means. Prospective IRB review and approval through the usual IRB process is required unless the criteria for the Requirements for Emergency Exemption from Prospective IRB Approval as described above are met. In addition, informed consent is required unless the criteria for the Informed Consent Exception Requirements are met.

The emergency use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.

### **4. Reporting to the IRB**

Emergency use of an investigational drug or biologic must be reported in writing to the IRB within 5 working days of such use. This report must provide documentation supporting each of the above listed criteria for Emergency Exemption from Prospective IRB Approval. A copy of the informed consent or documentation supporting each of the above listed criteria for the Informed Consent Exception Requirement must be attached. If available, additional supporting information such as a protocol, investigator's brochure or published reports of similar use should be included. The IRB will then review the documentation that is provided and determine whether the circumstances met FDA regulations.

Emergency use of a test article will be reported to the IRB as information. Data arising from emergency use may be used for research purposes only to the extent allowed by FDA regulations. Any subsequent use of the test article at the institution is subject to IRB review.

If using a medical device and an IDE for the use does not exist, documentation that the sponsor has been notified should be provided to the IRB, or if an IDE does not exist, documentation that

the FDA has been notified, should be provided. FDA notification should include a written summary of the conditions constituting the emergency, subject protection measures, and results.

## **5. Exception from Informed Consent for studies conducted in Emergency Settings**

Persons with life-threatening conditions who can neither give informed consent nor refuse enrollment in a study have diminished autonomy, and thus constitute a vulnerable population. Therefore special consideration and additional protective procedures are warranted for the IRB the review, approval, and conduct of research conducted in emergency settings.

FDA and OHRP regulations provide a narrow exception to the usual requirements, and that informed consent be obtained from human subjects, or their legally authorized representatives (LAR), prior to initiation of an experimental intervention. This exception applies to a limited class of research activities involving human subjects who are in need of emergency medical intervention, but who cannot give informed consent because of their life-threatening medical condition, and who do not have a legally authorized person to represent them. The intent of the regulation is to allow the safe and ethical conduct of research in life-threatening conditions for which available treatments are unproven or unsatisfactory, while establishing additional protections for the rights and welfare of subjects who cannot provide informed consent.

Note that these exception regulations DO NOT apply to research involving fetuses, pregnant women, and human in vitro fertilization and research involving prisoners. These regulations do not preempt state or local law. When a study is following DoD regulations, an exception from consent in emergency medicine is prohibited unless a waiver is obtained from the Secretary of Defense.

Principal Investigators who plan to conduct research protocols in an emergency setting where it may not be possible to obtain consent from the subject or their legally authorized representative, and when the research involves a Food and Drug Administration (FDA) regulated drug or device are strongly encouraged to consult with the Director of the IRB and the IRB Chair(s) in preparing their applications. The investigator may also wish to attend the IRB meetings where the protocol is reviewed to answer questions and concerns raised by the members of the Board. Meetings with other Institutional representatives, such as public affairs or legal affairs, may also be necessary.

In the protocol, the principal investigator must provide assurance and justification that following key conditions are met:

- a. The human subjects who will be studied will be in a life-threatening situation
- b. Available treatments for the condition under study are unproven or unsatisfactory

- c. Collection of valid scientific evidence is necessary to determine the safety and effectiveness of the proposed investigational interventions
- d. Obtaining informed consent from some or all subjects is not feasible because:
  - a. Some subjects will not be able to give informed consent as a direct consequence of their medical condition, for example they are unconscious;
  - b. To be maximally effective in saving life or limb, the investigational intervention must be administered before it is feasible to obtain consent from the subject's legally authorized representatives;
  - c. There is no reasonable way to prospectively identify, in a reasonable time frame, which individuals are likely to become eligible for participation in the study
- e. Participation in the research holds out the prospect of a direct benefit to the subjects
- f. The study could not practicably be carried out without the waiver of informed consent

In the protocol the principal investigator must also provide a detailed description of how the following **required** procedures will be carried out:

- a. **Concurrence of a Licensed Physician.** Because 21 CFR 50.24 permits an exception from the requirement for informed consent for a group of subjects, the case-by-case independent determination is replaced by the general concurrence of a licensed physician to the enrollment of potential subjects. This physician must be someone "who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation" (Sec. 50.24(a)). The option to use a consultant to the IRB provides flexibility, for example, when the physician member(s) cannot participate in the deliberation and voting due to conflict of interest. Because the documented concurrence of the physician is required for approval of these studies, the IRB will ensure that meeting minutes specifically record his/her affirmative vote.
- b. **Ongoing Attempts to Obtain Consent.** Researchers planning to conduct research that does not include the informed consent of all subjects must present a plan describing how they will attempt to obtain consent from the subjects and/or their legally authorized representatives on an ongoing basis throughout the conduct of the study and at the conclusion of the research. It is also required that information be provided about the clinical investigation to the subject's legally authorized representative or to a relative, if feasible, if the subject dies before consent has been obtained. Investigators must describe how they will document and summarize their attempts to contact family members to obtain their consent if obtaining informed consent is not feasible and a

legally authorized representative is not reasonably available; this information will be required at the time of continuing review.

- c. **Community Consultation.** The FDA requires that investigators will provide an opportunity for the community from which research subjects may be drawn so that they may understand the proposed clinical investigation and its risks and benefits and have an opportunity to ask questions, raise concerns, and voice objections. Thus, consultation with appropriate community representatives must occur before the research begins.

For example, the principal investigator could schedule a public meeting in the community to discuss the protocol. At least one member of the IRB must attend the public meetings to assess the public perception of the research. The IRB may wish to establish a panel of members of the community from which the subjects will be drawn to gain input. The IRB could add ad hoc members to the board who are not affiliated with the institution and are representative of the community; or develop other mechanisms to ensure community involvement and input into the IRB decision making process. It is likely that multiple methods may be needed in order to provide the supplemental information that the IRB will need from the community to review the proposal. The IRB will consider the plans for this community consultation in reviewing the investigation, and may decide, among other things, that it is appropriate to attempt to exclude certain groups from participation in the investigation, or that wider community consultation and discussion is needed.

- d. **Public Disclosure.** Appropriate public disclosure must occur before initiating the study, and also at the completion of the study. It is the responsibility of the principal investigator to disclose information to the public; however, the IRB is responsible for determining the information to be disclosed. This information could include, but may not necessarily be limited to, the information that is found in the informed consent document, the investigator's brochure, and the research protocol. The IRB will consider how best to publicly disclose, prior to commencement of the clinical investigation, sufficient information to describe the investigation's risks and benefits. Initial disclosure of information will occur during the community consultation process.

It is also necessary to provide comprehensive summary data from the completed trial to the research community in order to permit other researchers to assess the results of the clinical investigation. Sufficient information may be contained in a scientific publication of the results of the completed investigation; in other instances, a publication may need to be supplemented by additional information. Information to be disclosed must include the demographic characteristics (age, gender, and race) of the research population. Following publication, the IRB will be responsible for determining appropriate mechanisms for providing this information, possibly supplemented by a lay description, to the community from which research subjects were drawn.

- e. **A separate IND or IDE.** Protocols involving an exception to the informed consent requirement must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35 of this chapter.
  
- f. **Independent Data Monitoring Committee.** An independent data and safety monitoring committee is required to assure that if it becomes clear that the benefits of the investigational intervention are established, or that risks are greater than anticipated, or that the benefits do not justify the risks of the research, the investigation can be modified to minimize those risks or the clinical investigation can be halted.

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

The IRB determinations required by FDA regulation for an Exception from Informed Consent for Studies Conducted in Emergency Settings must be retained by the IRB for at least 3 years after completion of the study, and the records shall be accessible for inspection and copying by the FDA and the Office of Human Research Protections (OHRP) and as required by federal regulation.

If the IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under the FDA regulation for an Exception from 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. Informed Consent for Studies Conducted in Emergency Settings paragraph or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to the 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.

## XIII. Reportable Events

### 1. Unanticipated Problems

To help ensure the protection of the rights, safety, welfare and privacy of subjects, all **unanticipated problems** involving risks to subjects or others shall be promptly reported to the IRB. In addition, unanticipated problems shall be reported to the study sponsor, Office for Human Research Protections (OHRP), US Food and Drug Administration (FDA), Department of Defense (DoD) or other Department or Agency as required by federal regulation, the research protocol, or the research contract.

An unanticipated problem is any event, incident, experience, or outcome (including, but not limited to, **adverse events** and **serious adverse events**) which occurs in a research study and meets **ALL** of the following criteria:

- **Unexpected** in nature, frequency, or severity (not articulated in the study protocol, informed consent or Investigator's Brochure or not expected as a consequence of the natural history of a disease under study)
- **Related or possibly related** to participation in the research (there is a reasonable possibility that the event, incident, experience, or outcome may have been caused by the drug/device, procedures or interventions involved in the research )
- **Places subjects or others at a greater risk of harm** than was previously known or recognized (causes physical, psychological, economic, or social harm to a human subject; increases the risk of harm of any kind; or otherwise compromises subject's safety, rights, welfare, or privacy).

Reportable events are not limited to physical injury, but also include psychological, economic and social harm. Reportable events may arise as a result of the use of drugs, biological agents, devices, procedures or other interventions; or as a result of the use of questionnaires, surveys, observations or other interactions with research subjects. All **breaches of confidentiality** are reportable events. Reporting to the IRB is required regardless of the funding source or study sponsor.

Unanticipated problems, including those which may occur after the subject has completed or has withdrawn from the study, should be reported until the time of study closure.

All members of the research team share the responsibility for reporting unanticipated problems involving risk to subjects or others to the IRB and other applicable parties. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB, whether these reports are from a local site or from an external site conducting the same protocol.

The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others are reviewed to determine whether the report represents a change in the

risks and/or benefits to subjects, and whether any changes in the informed consent, protocol or other study-related documents are required.

## 2. Protocol Deviations

All [protocol deviations](#) shall be reported to the WFUHS IRB, the study sponsor, OHRP, FDA or other Department or Agency as required by federal regulation, the research protocol, or research contract, regardless of the funding source, and regardless of whether or not they constitute an [unanticipated problem](#) or [adverse event](#).

A protocol deviation is any event, action, or activity associated with the conduct or oversight of a human subject research study that **fails to comply (non-compliance)** with the approved study protocol or consent, IRB policies and procedures, federal agency regulations, or other applicable regulatory policies governing such research, regardless of whether or not it causes harm of any kind to subjects, increases the risk of harm, or otherwise negatively impacts their safety, rights, welfare, or privacy.

## 3. Non-Compliance

The WFUHS IRB is responsible for the protection of the rights, safety, welfare and privacy of human subjects participating in research projects that takes place at **Wake Forest Baptist Medical Center**. The Principal Investigator and all **study team members** are expected to comply with all ethical standards for the conduct of **human subjects research**, institutional policies, state and federal laws and regulations related to human subjects research, and any conditions placed on the conduct of the research activity by the IRB. All reports or allegations of non-compliance will be investigated and addressed by the IRB and/or the Institutional Official.

Upon notification of an allegation of potentially **serious** or **continuing non-compliance**, the following will occur:

### **Preliminary Determination of Suspension or Non-suspension**

The IRB Director, upon consultation and agreement by an IRB Chair, will determine if immediate suspension of study procedures and/or study enrollment is required for the specific research project in question, as well as for other research projects conducted by the investigator in question. This initial decision is based on preliminary review of available information, communication with the Principal Investigator (PI) involved in alleged noncompliance activities, and the seriousness of the allegations.

If the noncompliance activity is determined to not be serious or continuing:

- The issue will be resolved by discussions among the IRB Director, IRB Chair, Oversight and Outreach, the PI involved in noncompliance activities, the Department or Section Head, and the Institutional Official.

- The IRB Director will document the outcome of all deliberations and communications in writing. This report will include any sanctions or **corrective actions** required on the part of the investigator and the time frame for such corrective actions to occur.
- A written response from the PI acknowledging receipt of the report and describing actions to implement the recommended corrective actions will be required within **10 working days** from the date of the corrective report.
- The complainant will be provided information regarding the outcome of the investigation, as deemed appropriate by the IRB Director.
- IRB committees will be informed of non-serious and non-continuing noncompliance actions, **as they arise**, including the corrective recommendations and written responses from the PI. The PI or their designee should keep a log of non-serious, non-continuing noncompliance events, which should be **uploaded for IRB members to review at the time of continuing review**. Events that are reported individually and do not meet the definition of serious or continuing non-compliance will be reported to the IRB as **informational items on a future agenda**.

If the noncompliance activity is determined to be of a serious or continuing nature, further investigation by the IRB may be warranted.

If research activity suspension is warranted, the following will occur in addition to the actions listed above:

- The PI involved in noncompliance activities and associated study team members, Department or Section Head, and the Institutional Official will be notified in writing about the suspension.
- The PI involved in noncompliance activities will be required to respond to the inquiry findings within **2 working days** from the date of the written report, unless an extension is requested in writing and granted by the IRB Director.

### **Research Misconduct**

In cases that involve allegations of **research misconduct**, the IRB Director will notify the Institutional Official and the Research Integrity Officer for further action. This does not preclude the IRB Chair or any member of the IRB from independently contacting the Institutional Official about any allegation of research misconduct. Inquiries or investigations into research misconduct do not preclude IRB review and actions.

## **4. Reporting to External Agencies**

Institutional policy requires compliance with all applicable accreditation, local, state, and federal reporting requirements in the conduct of research involving human subjects. The IRB notifies appropriate officials when research falls under the purview of a federal regulatory agency and one or more of the following occurs:

- Unanticipated problems involving risks to subjects or others;

- Serious or [continuing noncompliance](#) with the regulations or requirements of the IRB;
- [Suspension](#) or [termination](#) of IRB approval for research due to noncompliance;

Reporting to regulatory federal agencies is not required if the Principal Investigator (PI) voluntarily closes down a study to new subject accrual or temporarily halts the research procedures. The IRB, IRB Chair, IRB Director, or administrative officials may recommend voluntary closure to the PI, but the PI makes the decision whether closure is appropriate. However, if the IRB or IRB Chair requires suspension or termination, then the incident may be reportable under this policy.

The Federalwide Assurance (FWA) with OHRP is restricted to research funded by the federal DHHS. However, the same process for conducting investigations and taking actions by the IRB will apply to all research regardless of funding source. All other reporting requirements listed below will remain in effect. The IRB reserves the right to voluntarily report any event that is not associated with federal funding to OHRP. Copies of reports will be shared with appropriate institutional and departmental representatives.

After completing an investigation, a report will be drafted promptly. It is the aim of the IRB to have a draft report sent to the appropriate agency within 30 days from the time the event is resolved to the satisfaction of the IRB. The report will be drafted by the IRB Director in consultation with the IRB Chair, an Oversight Specialist, the Assistant Dean for Regulatory Affairs & Research Integrity, and others as needed. All correspondence with any federal agency will be sent on behalf and with knowledge of the Institutional Official. Following this internal review process, the report will be signed and sent by the IRB Director.

### **FDA Regulated Research**

When research is regulated by the FDA, the IRB requires the PI to report to the sponsor, who should report to the FDA with a copy to the IRB. If the PI is also the sponsor, then the IRB requires that the PI report to the FDA. The IRB Director may choose to prepare and send the report of a suspension or termination directly to the FDA.

### **DHHS Funded Research**

If the DHHS conducts or funds the research, the IRB Director sends the report to the OHRP.

If an agency that is subject to the “Common Rule,” other than the DHHS, conducts or funds the research, the IRB Director sends the report to the agency as required by the agency and OHRP.

### **Record Retention**

The IRB Director maintains all correspondence relating to the serious or [continuing noncompliance](#). The IRB Director provides a copy of the federal report(s) and any final IRB actions to the staff, which are responsible for placing the report(s) in the IRB study file.

## 5. Other Items Reportable as a Safety Event

### Data and Safety Monitoring Board (DSMB) reports

All **Data and Safety Monitoring Board (DSMB)** reports must be submitted to the IRB within **30 calendar days of receipt** by the investigator or study team. These reports are initially reviewed by the HROS, who may thereafter request additional review by the IRB Executive Chair, the IRB Director, IRB members or non-IRB members with special expertise related to the event. The HROS may request more detailed information from the investigator(s), the sponsor, the study coordinating center, or DSMB/DMC.

If DSMB reports are expected but not received prior to the annual continuing review of a study, the convened IRB should not vote to approve the study without the appropriate updates and information provided by the DSMB.

### FDA 483 report

All **FDA 483 reports** should be reported to the IRB within **7 days of receipt**. The HROS will review each report to ensure that the safety, rights, welfare, and privacy of subjects have not been put at higher risk. FDA 483 reports will be assessed and processed in the same manner as DSMB reports.

### Audit/Monitoring Reports

All reports received from external auditors/monitoring visits should be reported to the IRB within **30 calendar days of receipt**. Examples of external auditors/monitors include representatives from the study sponsor, contract research organization (CRO), or federal agency. The HROS will review each audit report to ensure that the safety, rights, welfare, and privacy of subjects are protected. External reports will be assessed and processed in the same manner as DSMB reports.

Reviews conducted by Wake Forest University Health Sciences Oversight and Outreach are for the benefit of the investigator and are not reportable to the IRB. If significant deficiencies are noted during a review by Oversight and Outreach, then these deficiencies may require reporting to the IRB as directed by the HROS.

### Subject Complaints

Subject complaints may be submitted to the IRB through the eIRB system (**timeframe?**). When a complaint is filed, the HROS reviews the complaint, the actions taken by the study team in response to the complaint, and the proposed **management plan** to prevent similar complaints in the future. After review by the HROS, the complaint will either be reported to the Board as information at a scheduled meeting or may be placed on an upcoming IRB meeting agenda for discussion. Complaints may also be forwarded to the IRB Director or other appropriate institutional officials based on the nature of the complaint.

### Other reports

Updated study safety information or reports that address the risk or potential benefits of the research should be reported to the IRB. If the reports warrant a change to the research (i.e. informed consent form, recruitment documents, study status, etc.), then an amendment should be submitted concurrently. Examples of “other” reports include:

- FDA safety alerts
- Relevant publication in the literature or other findings
- Any information that requires prompt reporting according to the protocol or the study sponsor
- Incarceration of a subject in a protocol not approved to enroll prisoners.

Please note that the following reports should always be submitted as amendments, not as safety events:

- Revised Investigator’s Brochure
- Study Summaries (Summaries of study data such as enrollment numbers, drug toxicities, safety events, etc.)
- Annual reports.

## 6. Investigator Requirements for Reporting to the IRB

Reports should be submitted via eIRB using the IRB Safety Event reporting process. All reports should include a complete description of the event, an explanation as to why it occurred, and a [corrective action plan](#) to prevent recurrence. The following must be reported to the IRB as soon as possible, but no later than 7 days, after the investigator or other members of the study team becoming aware of the event:

- All unanticipated problems involving risks to subjects or others that occur in a study overseen by the Wake Forest IRB
- Unanticipated problems involving risks to subjects or others that occur at another site (not under the oversight of the WFUHS IRB) conducting the same protocol
- Any protocol deviations that **do** meet the definition of an unanticipated. Events, incidents, experiences, outcomes, or substantive changes in the research protocol or informed consent process/document which increases the risk of the research or otherwise threatens the safety, rights, welfare or privacy of subjects. Examples include, but are not limited to:
  - Any **breach of confidentiality** or privacy
  - Incarceration of a study subject in a study not approved to enroll prisoners
  - An unexpected natural disaster, such as a flood or tornado that destroys records or specimens
- Any changes that were made to the research without prior IRB approval to mitigate an imminent risk of harm to the subjects.

Protocol deviations that **do not** meet the definition of an **unanticipated problem** should be entered into the study [Protocol Deviation Log \(link\)](#) and submitted to the IRB at the time of

annual continuing review. If the IRB subsequently determines that any of the deviations recorded on the log constitute **serious** or **continuing non-compliance**, an appropriate [corrective action plan](#) will be requested.

The following should NOT be reported to the IRB:

- Any event, incident, experience, or outcome that does not meet all of the criteria for an unanticipated problem involving risks to subjects or others as defined above
- External [adverse event](#) reports when all subjects at this site have completed study participation, and the [adverse events](#) do not require the notification of previously enrolled subjects
- Unanticipated problems involving risks to subjects or others that occur at another site as part of a study that has not been approved by the WFUHS IRB.

## 7. IRB Responsibilities for Review and Response

All [unanticipated problems](#) involving risks to subjects or others that occur in a study that has been **approved by the WFUHS IRB** are initially reviewed by a Human Research Oversight Specialist (HROS) or designee, who is also an IRB member. The HROS makes an initial assessment of whether:

- The report represents an unanticipated problem involving risks to subjects or others
- The **management plan ([corrective action plan/management plan](#))** proposed by the investigator is appropriate to ensure the safety, rights, welfare and privacy of subjects
- Risks to subjects are minimized
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge that may reasonably be expected to result
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

When a deviation or unanticipated problem involves no more than minimal risk to the subject or others, the HROS will review the report based on the criteria listed above. The HROS may concur with the management plan or determine that additional action is needed to protect subjects. The event will be assigned to an IRB agenda where Board members can review the event and management plan once the preliminary review by the HROS is complete.

If the deviation or unanticipated problem is determined to be more than minimal risk to the subject or others, the HROS may request more detailed information from the investigator(s), the sponsor, the study coordinating center, or [Data Safety Monitoring Board](#) (DSMB). If more detailed information is needed, the safety event will be returned to the study team with specific concerns outlined. The HROS may consult with IRB members or non-IRB members with special expertise related to the event. The report and any comments, findings or supporting information will be placed on the agenda for review by an IRB Board. When reviewed by an IRB Board, information is provided through the eIRB system to the primary reviewer, as well as all other board members. If

the IRB agrees that the report represents an event involving risks to subjects or others, the IRB will then determine whether:

- The proposed response is appropriate to ensure the protection of the safety, rights, welfare and privacy of subjects
- Risks to subjects are minimized
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge that may reasonably be expected to result
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- If the HROS determines that protocol deviation does not constitute an unanticipated problem, violation of IRB policies and procedures, or other actionable/reportable event, then it will be processed by expedited procedures and reported to the Board as information at a scheduled meeting. No additional action on the part of the principal investigator or study team will be required.

If the HROS determines that protocol deviation could constitute continuing or [serious noncompliance](#), then the HROS will place the report and any comments, findings, or supporting information on the agenda for review by an IRB Board. If the Board thereafter determines the report represents continuing or [serious noncompliance](#), it will review the adequacy of any proposed [corrective action plans](#) to ensure the protection of the safety, rights, welfare and privacy of subjects and/or enumerate the elements of an acceptable [corrective action plan](#) and communicate them to the principal investigator and study team.

If the HROS finds that the protocol deviation is reportable to external agencies, the HROS will advise the IRB Director, who will be responsible for executing the appropriate regulatory reporting.

If the HROS finds that the protocol deviation constitutes a HIPAA violation, a security breach, or possible research misconduct, these concerns will be forwarded to the appropriate institutional oversight bodies.

The IRB has the responsibility for the protection of subjects' safety, rights, welfare and privacy when reviewing unanticipated problems. IRB actions may include, but are not limited to:

- Acknowledgment/acceptance without further recommendation
- Request for further clarification from the investigator
- Request modifications to the protocol, consent forms, or study procedures
- Require notification of current subjects
- Modification of the continuing review schedule
- Monitoring of the research and/or consent process
- Referral to other organizational entities
- [Suspension](#)/termination of the research.

## **XIV. Multi-center studies**

All human subject research in which Wake Forest faculty or staff are engaged must be reviewed and approved by the Wake Forest School of Medicine IRB or another designated IRB prior to the initiation of the research. An off-site IRB, that serves as the IRB-of-record for Wake Forest has the same authority as an on-site IRB and all determinations and findings of the off-site site are equally binding on all research under the authority of the organization.

In the conduct of cooperative research projects, Wake Forest acknowledges that each organization is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations. All facilities participating in a study involving human subjects should receive adequate documentation about the study to protect the interests of the study participants.

### **1. Reliance on an Independent/Central IRB**

The use of an independent/central IRB is optional for industry supported studies. Investigators may wish to rely on an external IRB for some studies, but not others, or may choose to work with some central IRBs but not others. The IRB Director in consultation with IRB chairs and other designees will be responsible for determining when the Wake Forest IRB may cede review to an external IRB.

After submitting an application package to an external IRB, the investigator must satisfy the Wake Forest application requirements for externally reviewed studies. The mechanism to submit an application is through the facilitated review option in eIRB. A facilitated review submission is used to confirm completion of all institutional requirements (e.g. radiation safety, COI, biosafety, etc) and for tracking purposes. Investigators approved through an external IRB review must still report local unanticipated problems, complaints, non-compliance, substantive study modifications, changes in study personnel, and annual summary reports to the Wake Forest IRB. The external IRB must copy the Wake Forest IRB on all determinations of serious or continuing non-compliance and unanticipated problems involving risks to subjects or other.

In a similar process for single center review the research is responsible for the following actions when review is ceded to another organization:

- Researchers must cooperate with the responsibilities and determinations established by the reviewing IRB and provide information to them in a timely manner.
- Researchers must disclose conflicts of interest according to the agreed upon process between Wake Forest and the reviewing IRB.
- Researchers must report changes to the reviewing IRB prior to implementation unless in the case to eliminate apparent immediate hazards to the participants. Changes that only affect the Wake Forest site are still under the authority of the external IRB and must be approved by that entity and reported to the Wake Forest IRB as information prior to implementation.
- Researchers will not enroll participants in research prior to review and approval by the IRB of record and the Wake Forest IRB.

- When responsible for enrolling participants, researchers will maintain records of consent for each participant or their legally authorized representative.
- Researchers will provide data safety monitoring reports to the reviewing IRB according to their policy.
- Researchers will report non-compliance, complaints, deviations or other safety events in accordance with the reliance agreement and the policies of the reviewing IRB.

The Wake Forest IRB will also evaluate a facilitated submission. The key points that will be considered are as follows:

- Completeness and consistency across study documents
- Documentation of approval from the IRB-of-record
- Review of investigators and study staff to ensure appropriate training, education, and COI disclosure
- Review of institutional requirements (radiation safety, pharmacy, etc)
- Make applicable determinations of a privacy board for HIPAA waivers and information
- Local context information included in the consent form

Once the above listed information is satisfactory, then the Wake Forest IRB will enter into an agreement with the IRB-of-record to rely upon the previously established approval of the study.

In a similar process for single center review the Wake Forest IRB is responsible for the following actions when ceding review to another organization:

- Notifying the reviewing IRB when local policies that impact IRB review are updated.
- Ensuring that officials of Wake Forest may not approve research that has not been approved by the reviewing IRB.
- Conduct monitoring of studies in cooperation with the IRB of record.
- Communicating circumstances to the reviewing IRB that must take into account additional regulatory requirements such as DoD or other agencies.

## **2. Reliance on the NCI CIRB**

Wake Forest is a participant in the National Cancer Institute's (NCI) Central Institutional Review Board (CIRB) Initiative for cooperative group protocols/studies that have been reviewed and approved by the CIRB. An authorized Wake Forest representative submits the necessary documentation to maintain institutional registration with the CIRB.

The NCI CIRB defers responsibility to local institutions to conduct any reviews necessary under HIPAA. The CIRB does accept institutional boilerplate language for HIPAA authorizations. Requests for a limited HIPAA waiver for use of PHI to identify and/or screen potential candidates should be submitted to the Wake Forest IRB via the facilitated review process. The NCI CIRB relies on local institutions to identify potential conflicts of interest and to develop appropriate conflict management plans. Investigators must submit conflict management plans or other

relevant information to the NCI CIRB as part of the study-specific worksheet about local context. With consultation from the study investigators and staff, an authorized representative of the institution will submit the necessary materials to the NCI CIRB. The investigator will be responsible for submitting local materials to the Wake Forest IRB in the same manner and detail as previously described when using an independent/central IRB.

### **3. Reliance on other academic institutions**

When employees or agents of an investigator-initiated human subjects research study collaborates with other institutions or with individual investigators, each collaborating institution and/or investigator engaged in the conduct of human subjects research must obtain IRB approval for the research. Additional guidance on the engagement of institutions in human subjects research can be found on the OHRP website. IRB approval may be dually sought or a reliance relationship may be executed.

When a Wake Forest investigator would like to rely on the approval of an IRB from another institution, a request for facilitated review must be submitted in the manner and sequence previously described. Upon submission an appropriate Authorization Agreement may be executed with the reviewing IRB, by the IRB Director, in consultation with the IRB Chairs.

### **4. Use of an external IRB in the case of COI**

An agreement has been executed and regulatory filings completed to allow Copernicus IRB to function as a reviewing IRB for Wake Forest. This provides the opportunity to have an independent IRB review of human research studies in situations where review by an independent IRB is determined appropriate.

Only at the request of the COI or IRB office may Copernicus IRB be utilized. Notification of the institution of the study should be completed through the facilitated review process as previously described. The following are circumstances when a research study may be recommended for review by Copernicus IRB:

- The Conflict of Interest in Research Committee recommends review by an independent IRB as part of a management plan for an investigator, whose research proposals present as individual or institutional conflict of interest
- Investigator identifies an institutional conflict of interests and contacts the IRB
- The institution identifies other compelling reasons for which review of a study by the Copernicus IRB would be in the best interest of the institution.

When institutional COI is identified on industry sponsored studies, the cost will be covered by the study budget.

When the IRB lacks the expertise to conduct the review of the study, Wake Forest will pay the costs of Copernicus.

On PI initiated studies where there is an identified institutional conflict of interest, the responsibility for Copernicus costs will be determined by the Dean of the Wake Forest School of Medicine.

## **5. Reviewing IRB**

The Wake Forest IRB may serve as the IRB-of-record for external sites. When the Wake Forest IRB serves as the IRB-of-record, a representative of the study team will be responsible for submitting materials on behalf of collaborating sites. Since only people with Wake Forest log-in credential have access to eIRB, local investigators will be responsible for relaying information to and from the Wake Forest IRB.

The IRB Director, in consultation with the IRB chairs and other institutional representatives, will determine when Wake Forest could serve as the IRB-of-record for external sites.

When research oversight of the Wake Forest IRB is extended to other sites, the external investigators will be responsible for providing information about local or state context, as applicable, a draft consent form with site specific information, and documentation of training and qualifications of the investigators. The Wake Forest IRB will apply the same standards and regulations when reviewing a multi-site study, as required for a single site project, including but not limited to management of IRB membership, criteria for approval, and management of conflicts of interest.

When the Wake Forest IRB is serving as the single/central IRB, sites may be added to a study through an amendment process. Sites will be asked to provide information about local context that may include training and qualifications of local investigators, state, and institutional policies on the involvement of vulnerable populations, and specific required language in the informed consent document. It is possible to add sites to a study by expedited procedures at the discretion of the IRB Director or designee. The convened IRB may evaluate the addition of a site if there are concerns regarding the investigator's qualifications, such as recent 483 citations, known conflicts of interest, or invalid licensure.

## **6. Reviewing site responsibilities**

When the Wake Forest IRB serves as the single/central IRB it retains authority over the following situations:

- To decide whether a research conflict of interest and its management, if any, allows the research to be approved.
- To review unanticipated problems involving risks to participants and others.
- To suspend or terminate IRB approval.
- To notify the researcher and organizations of its decisions, consistent with any reliance agreements.
- To make available relevant IRB records, such as minutes, approved protocols, consent documents, and other records at the request of the relying institution.
- To request an audit of research being reviewed.

- To make relevant IRB policies readily available, and to communicate when updates are made.
- To specify the contact person and contact information for the reviewing IRB for researchers and participants to obtain answers to questions, express concerns, and convey suggestions regarding the IRB.

## **7. Individual Investigator Agreements**

The IRB can enter into an Individual Investigator Agreement (IIA) with individuals with whom the institution and faculty collaborate on a single research project.

When collaborating with an investigator, an IIA should identify the following:

- The name of the institution approving the research
- The Institution's FWA number
- The title of the project
- The Individual Investigator's Name

The IIA established a written understanding defining the scope of responsibility of the investigator for the research study involved. The investigator must review and understand HHA regulations for the protection of human subjects at 45 CFR 46, as well as the requirements of federal, state, and local laws. For research involving FDA regulated products, the investigator must be in compliance with the requirements defined in 21 CFR 50, 56, 312, 812, and ICH-GCP.

IIAs are signed by the IRB director or designee. IIAs are tracked and included in the study files for documentation.

Investigators wishing to collaborate with unaffiliated individuals should contact the IRB to determine whether an IIA is appropriate. Individual investigators must have proof of human subjects protection training, preferably CITI training, prior to executing an agreement.

## **8. SMART IRB**

Wake Forest has signed the master agreement to participate in the SMART IRB initiative. When utilizing the SMART IRB reliance systems, the processes for notification and reporting are the same as listed previously when either reviewing or relying on another institution.

## **9. Federal policies and regulations**

The institution is aware of the NIH policy regarding the use of single IRB and will apply this policy effective in January 2018. The institution is also aware of the revisions to the Common Rule which require use of single IRB for all federally funded projects that is effective in January 2020.

For NIH sponsored studies, an authorization agreement documents the respective authorities, roles, responsibilities, and communication between an organization providing the ethical review and a participating organization relying on a review IRB. The NIH policy applies to awardees in the United States and participating sites in the United States. The requirement for single IRB review does not apply to organizations outside the United States. Awardee organizations are

responsible for ensuring appropriate documentation of authorization agreements and maintenance of such documents. The prime awardee is responsible for any additional requirements including but not limited to clinicaltrials.gov registration, certificates of confidentiality, and NIH data sharing. With limited documented exceptions, sites are expected to rely on the single IRB.

### **10. Working with a non-accredited organization**

Wake Forest has been continuously accredited by AAHRPP since 2011. The institution prefers to partner with other accredited institutions, however understands that research may be done in collaboration with institutions that are not accredited. In some cases, a non-accredited institution may be the reviewing IRB because they are the prime awardee of a federal grant or the majority of research will be conducted at their site. In which case, the Wake Forest researcher will follow the same procedures for notification of the Wake Forest IRB, and the IRB Director or designee will evaluate the study proposal and the level of risk to determine if a reliance arrangement can be established.

## **XV. Research involving vulnerable population**

### **1. Research involving Pregnant Women, Human Fetuses, and Neonates**

Pregnant women may be involved in several categories of research. IRB duties differ in each category, but the primary objectives are assessing: (1) whether the research holds out the prospect of direct benefit for the mother's health or for the fetus; and (2) the risks to the woman and to the fetus or infant. These requirements do not apply when the enrollment of pregnant women is entirely coincidental and bears no relationship to the research (e.g., a minimal risk survey of 1000 respondents and 1 happens to be pregnant).

If abortion is involved, the investigators may have no part in either the decision to abort or decisions about the timing or the method to be used; no change in the abortion procedure that would present more than minimal risk to the fetus or its mother can be introduced for research purposes. No monetary or other inducements (e.g., free care) may be offered to a woman to induce her to terminate her pregnancy for research purposes.

The IRB will ensure that research involving pregnant women or human fetuses comply with the requirements of Subpart A of 45 CFR 46 and Subpart B of 45 CFR 46. Research involving pregnant women or human fetuses will only be approved when the conditions outlined in 45 CFR 46.204 (a-j) have been met.

Research that is not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates will be sent to the Secretary of HHS for review. The Secretary will determine the approvability of the research based on the conditions stated in 45 CFR 46.207(b).

#### **Research involving neonates of uncertain viability and nonviable neonate**

Research involving neonates of uncertain viability or nonviable neonates will be approved only when the applicable conditions outlined in 45 CFR 46.205(a-d) have been met.

#### **Informed Consent**

The legally effective informed consent for research will be obtained from both [parents](#) (if necessary) of the neonate is obtained in accordance with Subpart B of 45 CFR 46 and institutional policy. The waiver and alteration provisions of 45 CFR 46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary 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. (45 CFR 46.205(c)(5))

#### **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 of subparts A and D of 45 CFR 46.

## 2. Research Involving Prisoners

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, or under house arrest. [45 CFR 46.303(c)]

The regulations covering research involving prisoners apply not only to research that targets prisoners or the prison setting, but also to subjects who become incarcerated following their enrollment or subjects for whom their incarceration is coincidental with their research involvement, (e.g., a prisoner with cancer enrolled in a treatment-oriented study that involves no other prisoners).

The primary issue surrounding the participation of prisoners in research is whether prisoners have a real choice regarding their participation in research, or whether their situation prohibits the exercise of free choice. A secondary issue is whether confidentiality of participation and of data can be adequately maintained in the prison. These issues must be evaluated by both the IRB as well as the North Carolina Department of Correction (DOC), for studies that involve its prisoner population. The PI is responsible for communicating with the DOC prior to submission of an IRB application.

In addition to problems of undue inducement, the involvement of prisoners in research raises questions of burden and benefit. Prisoners should neither bear an unfair share of the burdens of participating in research, nor should they be excluded from its benefits, to the extent that voluntary participation is possible.

In light of the issues and constraints associated with prisoners, the IRB will ensure that all research that involves prisoners complies with the additional safeguards and requirements set forth in Subpart C of 45 CFR 46. Research will only be approved if all conditions outlined in 45 CFR 46.305 and 45 CFR .306 have been satisfied.

**Minimal risk**, as defined for studies involving prisoners, is 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. In assessing risk to prisoners, the IRB should ensure that the risks involved in the research are equivalent to risks that would be accepted by non-prisoner volunteers. [45 CFR 46.303 (d)]

**Confidentiality** is extremely difficult to maintain in a prison environment. In prisons, people do not move about freely; the movements of prisoners are carefully tracked. When inmates are moved around (e.g., to go to a research appointment), everyone will know about it. Prison

records, including health care records, are accessible to persons who in other settings would not have access to such personal information, thus compromising the security of confidential information.

Generally, research involving prisoners does not qualify for expedited review; however, in the event that such a research study does qualify for expedited review, a prisoner representative should be one of the designated reviewers. The exemptions under 45 CFR 46.101 do not apply to research involving prisoners.

### **Responsibilities of the IRB**

If the IRB is to review a study involving the enrollment and participation of prisoners, then it must invoke the prisoner roster to the appropriate board for review, consistent with the requirements of 45 CFR 46.107. A prisoner representative must be present for the discussion and vote of all studies involving prisoners. The prisoner representative is not required if no protocols on the agenda involve prisoners, and will not be counted toward quorum unless needed to review a prisoner application.

For research reviewed by expedited procedures (no greater than minimal risk) involving interaction with prisoners (including obtaining consent from prisoners):

- Research involving prisoners involving interaction with prisoners (including obtaining consent from prisoners) may be reviewed by the expedited procedure, if a determination is made that the research is minimal risk for the prison population being studied or included.
- The prisoner representative must concur with the determination of minimal risk.
- The prisoner representative must review the research as a reviewer or consultant. This may be as the sole reviewer or in addition to another reviewer, or in place of another reviewer as appropriate.
- Review of modification and continuing review must use the same procedures for initial review using this expedited process including the responsibility of the prisoner representative.

For research reviewed by the expedited procedure that does not involve interaction with prisoners (e.g. existing data or record review):

- Research involving prisoners that does not involve interaction with prisoners may be reviewed by the expedited procedure, if a determination is made that the research is minimal risk for the prison population being studied or included.
- The prisoner representative may review the research as a reviewer or consultant if designated by the IRB chairs, but review by the prisoner representative is not required.
- Review of modification and continuing review must use the same procedures for initial review using this expedited process including the responsibility of the prisoner representative.

**Prospective Approval:** When submitting an IRB Application for involving prisoner subjects (or those likely to be detained) for prospective IRB review and approval, the PI must describe the prisoner-subject population planned for, including (i) the types of ‘involuntary confinement, detention, or incarceration’, (ii) the names/types of ‘penal institutions or alternative facilities’ with which he or she has established a relationship, and (iii) if enrollment is planned through the facility versus the relationship with the facility established in anticipation of an enrolled subject becoming a prisoner (in the case of the later, it should be clear that prior experience with research subjects necessitates the inclusion of prisoner-subjects).

**Amended Approval:** When a specific research subject becomes incarcerated and the IRB has not previously approved the research to involve prisoners, all research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease immediately until the requirements of subpart C have been satisfied (unless it is determined to be in the best interest of the subject to continue). The Principal Investigator MUST IMMEDIATELY notify the IRB of this event. The principal investigator is also responsible for amending the consent form and re-consenting the subject if they wish to continue participation in the study, prior to continuing study interventions or interactions. Please see the consent template for specific language to be included.

#### **Certification of prisoner research**

Institutions that conduct DHHS-supported research involving prisoners as human subjects must take several steps to certify that the research is permissible according to federal regulations. The institution must certify to OHRP that the IRB has made the seven findings required under 45 CFR 46 305(a), including the finding that the proposed research represents one of the permissible categories of research under 45 CFR 46 306(a)(2). The institution must send OHRP a certification letter to that effect which should include the name and address of the institution and specific identification of the research protocol including the relevant grant number.

### **3. Children Involved in Research**

The regulations outlined below apply to all research subjects who have “not attained legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.” In the state of North Carolina, a [minor](#) is defined as a resident under the age of 18 unless he or she is emancipated by the court, in the armed forces, or legally married.

The Children’s Health Act of 2000 requires that research “involving children that is conducted, supported, or regulated by the Department of Health and Human Services (DHHS) be in compliance with subpart D.” The IRB is considerate of the National Institute for Health’s (NIH) requirement of the inclusion of children in research and will assess the inclusion of children in research only when their participation is necessary to answer the scientific question being evaluated.

Research involving children can be considered exempt from further IRB review per the regulations meeting the definition of exempt research. However, the exemption for research “involving the use of educational tests, survey procedures, interview procedures, or observation of public behavior” cannot be used for research involving children unless the research is restricted to “observation of public behavior when investigators do not participate in the activities being observed.” Research involving children can be expedited in accordance with the regulations for the expedited review of research.

All research involving children will comply with the additional safeguards and requirements set forth in Subpart D of 45 CFR 46 and Subpart D of 21 CFR 50. Research involving children will only be approved by the IRB when the applicable statutes have been met. Research that is not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health of a child will be sent to the Secretary of HHS for review. The Secretary will determine the approvability based on the criteria established in 45 CFR 46.107(a-b) and 21 CFR 50.54 (a-b).

#### **Requirements for [assent](#) and parental permission**

Adequate provisions must be made for obtaining the permission of parents or guardians and for soliciting the assent of children, when in the judgment of the IRB, the children are capable of providing assent. In determining whether children are capable of assenting, the IRB will take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. The determinations that assent is not appropriate for some or all children involved in a study, and thus not required, will be documented in the meeting minutes. The IRB will document, in the minutes and the approval letter, for which children the waiver of assent is applicable. Generally, the IRB expects assent to be collected on all research subjects 7 years of age and older unless waived by the IRB.

When a child who was enrolled in research with parental or [guardian](#) permission subsequently reaches the legal age of consent to the procedures involved in ongoing research, the subject’s participation in the research is no longer regulated by the requirements of 45CFR46.408 regarding parental or guardian permission and subject [assent](#). Unless the Institutional Review Board (IRB) determines that the requirements for obtaining informed consent can be waived, the investigators should seek and obtain the legally effective informed consent, as described in the regulations from the now-adult subject for any ongoing interactions or interventions with the subjects.

When parental or guardian permission is obtained, it must be documented in accordance with 45 CFR 46.117 and 21 CFR 50.27 and should include the requirements for informed consent found at 45 CFR 46.116(a)(1-8) and 21 CFR50.25(a)(1-8) and any additional elements deemed necessary. The IRB will also determine whether permission is needed from one or both parents based on the criteria established in Subpart D of 45 CFR 46 and Subpart D of 21 CFR 50.

When determining who other than a parent may consent on behalf of a child, the IRB will take into consideration who under the applicable law of the jurisdiction meets the definition of a guardian. In instances where this may take place outside the state of North Carolina additional consultation will be sought to determine what is appropriate within the jurisdiction.

#### **IRB Waiver of [Assent](#) and Parental Permission**

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the [assent](#) of the children is not a necessary condition for proceeding with the research.

Even when the IRB determines that the subjects are capable of assenting, the IRB may still waive the [assent](#) requirement as permitted under 45 CFR 46.116(d)(1-4) and 21 CFR 50.55(d). Or if the intervention or procedures holds out the prospect of direct to the health and well-being of a child and is available only in the context of research, the IRB may waive the requirement for [assent](#).

The IRB may waive the requirements for obtaining parental or [guardian](#) permission if it makes and documents the findings under either 45CFR46.116(c) or (d). In addition to the provisions for waiver contained in 46.116(c) and (d), if the IRB determines that a research protocol 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), it may waive the parental permission requirements provided that an appropriate mechanism is in place to protect the children, and provided that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate substitute mechanism (for example, appointing a child advocate or an [assent](#) monitor) for protecting children participating in research would depend on the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and the child's age, maturity, status, and condition.

#### **Wards of the State**

Children who are wards of the state may be included in research that presents minimal risk or studies that involve greater than minimal risk with prospect of direct benefit. If children who are wards of the state will be included in research that is greater than minimal risk and no prospect for direct benefit, the IRB must determine and document that such research is

- Related to their status as wards; or
- Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as participants are not wards.

If children who are wards of the state are to be included in research with no prospect of direct benefit, the IRB shall appoint an advocate for each child who is a ward. It is the responsibility of the principal investigator to locate someone who can serve as an advocate and who possesses

the expertise to be an advocate; however, the determination of the role of the advocate is determined through an appointment by the IRB.

### **Advocates**

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 throughout the duration of the child's participation in the research. This includes ensuring that to the extent possible, the child understands what will be required of him or her during the research, and that if capable, the child provides his or her [assent](#) to participate. Acting in the best interests of the child could include evaluating the ongoing impact of the research study on the child. The advocate should represent the individual child subject's interests throughout the child's participation in the research. This added protection is intended to ensure that the ward, who is particularly vulnerable, is not exploited, coerced, or subjected to undue influence or harm in the course of the research. HHS regulations further require that the advocate not be associated in any way (except in the role of advocate or member of the Institutional Review Board (IRB)) with the research, the investigator(s), or the guardian organization.

If children who are wards are to be included in any research study, the investigator must provide the IRB with detailed information about the proposed permission/[assent](#) process, as well as the identity and authority of individuals who will provide permission for the [Ward](#) subjects. The information must be submitted to the IRB with the original application or via an amendment if the investigator later determines he/she wishes to enroll a ward of the state.

As part of the protocol application process, investigators will be asked if at the time of submission of the application there is a likely possibility that a protocol could involve children who are Wards of the State as potential research subjects, and if so, does the investigator plan to recruit Wards. If the investigator indicates a possibility that a protocol could involve Wards and the investigator wishes to offer the protocol to Wards, the IRB will make the required regulatory findings.

If there is a possibility that Wards may be included in the research and the risk/benefit classification is minimal risk or greater than minimal risk with a prospect of direct benefit, the IRB reserves the right to require reporting to the IRB of the enrollment of such wards and the appointment of an advocate as necessary. However, enrollment of wards in research that is minimal risk or greater than minimal risk with a prospect of direct benefit would not require the appointment of an advocate.

If the investigator does not initially anticipate the inclusion of Wards in the protocol, but circumstances change or a situation arises where the investigator wishes to include a Ward, a protocol amendment must be submitted to the IRB so that any required regulatory requirements may be fulfilled.

### **Legally Authorized Representatives**

Principal Investigators are responsible for determining any changes in a legally authorized representative (LAR) for children participating in research. The investigator will inform the IRB which methods will be used for determining changes in the status of the LAR. This could include but is not limited to the following:

- periodically asking the accompanying adult if there has been a change in guardianship;
- including within the informed consent that the [guardian](#) should inform the investigator if here has been a change in status;
- other methods that are reasonably designed to ensure prompt notice of such changes, sufficient to protect the rights of children as human subjects under the circumstances presented in the study.

A change in the LAR status requires obtaining permission from the newly appointed LAR in order for the child to continue participation in the research.

Investigators are asked at the time of continuing renewal if the study has enrolled vulnerable populations in the past year which includes and is not limited to children and Wards of the State. If an investigator answers yes and describes enrollment of Wards of the State, and if this information was not indicated in the initial application, the IRB will reassess the regulatory determinations for the research and document findings. The investigator will be subject to the requirements above.

Please note that parents of children in Department of Social Services (DSS) care or custody may, and most often do, retain the right to consent for their child to participate in medical or psychological procedures and research. However, depending on the circumstances, DSS and even court consent may also be required. If the parent(s) has sole legal custody, only parental permission via consent is necessary for the child to participate in a research study. If DSS has sole or joint legal custody and the parent(s) consent for their child to participate in a research study, DSS is likely to consent as well absent special circumstances. DSS may withhold consent in situations where the parent cannot be located, where a petition to terminate parental rights has been granted, when a child has been surrendered for adoption, or for reasons specific to a family's or child's circumstances and needs. If DSS withholds consent based solely on the absence of the family, they may seek judicial approval for the child's participation; it is unlikely DSS will permit participation based solely on its administrative consent where a parent who has the right to consent (provide permission) cannot be located.

For situations in which a child enrolled in the research study is placed in the care of DSS, the investigator is required to notify DSS of the research so they are aware of the participation and any questions can be addressed. In addition, if a child begins a study under DSS custody without permission from the parent and the child is later reunited with the parent, parental permission must be obtained from the parent in order for the child to continue his/her participation in the study.

All IRB determinations including the need for an advocate will be documented in the minutes of the IRB meetings.

#### **4. Research involving adults with diminished capacity to consent**

The IRB will evaluate whether the study may involve individuals that have diminished decision-making capacity. This could include individuals that are under the influence of drugs or alcohol, suffering from degenerative diseases affecting the brain, terminally ill, or have disabling physical handicaps.

In addition to considerations associated with the criteria for approval, the IRB will evaluate the following additional points when reviewing research involving adults with diminished decision-making capacity:

- a. Whether the research could be conducted without these individuals.
- b. How the study addresses the needs of this vulnerable population
- c. Adequacy of the proposed initial and ongoing consent and [assent](#) processes to include:
  - i. The proposed plan for the assessment of the capacity to consent.
  - ii. The plan to obtain [assent](#) from the participant.
  - iii. The consent process for the legally authorized representative
  - iv. The process to ensure the legally authorized representative understands their role and responsibilities as the individual that is making decisions on behalf of the participant.
- d. Who under state or local law meets the DHHS and FDA definition of “legally authorized representative” will be determined under the applicable law of the jurisdiction in which the research will be conducted. In instances where research will take place in jurisdictions outside of North Carolina (including other states and other nations), the IRB will consult with legal counsel or representatives within the applicable region to determine the requirements within the specific jurisdiction. When research is conducted at Wake Forest, the listing of who may serve as an LAR is consistent with institutional policy found at\_\_\_\_\_.

#### **5. Students as research participants**

The IRB does permit students to be enrolled in studies, however additional precautions should be in place to neither coerce nor suggest undue influence. The status of a student’s relationship with the institution should not be jeopardized if a student declines or withdraws from a research study.

#### **6. Economically or Educationally Disadvantaged**

The IRB will review research targeted at groups of individuals who are economically or educationally disadvantaged to assure that participation is voluntary, free of coercion, duress, or undue inducement.

In reviewing research in which economically or educationally disadvantaged individuals are likely to be recruited, the IRB will specifically consider the following:

- a. Recruitment and consent processes provide sufficient detail for IRB members to assess the voluntary participation of participants.
- b. All study documents, including materials read to participants or provided in writing, are appropriate to the population and will be easily understood.
- c. Any reimbursement for participation is reasonable in relation to the time required.

## **XVI. HRPP**

### **1. Relationship of the IRB to the Research Community**

The IRB does rely on specialty review of a number of ancillary groups listed below. Approval by all applicable groups must be obtained prior to IRB approval.

**Institutional Biosafety Committee (IBC):** On issues regarding the safe and appropriate use of biological agents, the IRB interacts with the IBC. Approval of both committees is required prior to initiation of the study.

**Medical Radiation Safety:** On issues regarding the safe and appropriate use of radiation, the IRB interacts with the Radiation Safety Committee. Approval of both committees is required prior to initiation of the study.

**Clinical Research Unity (CRU):** Protocols that propose the use of the CRU by subjects should be evaluated and approved by the CRU. The purpose of this review is for space and resource utilization. Approval of CRU and IRB is required prior to initiation of the study.

**Cancer Center Protocol Review Committee (PRC):** Protocols involving oncology patients should be submitted and approved by the PRC. Approval of the PRC and IRB is required prior to initiation of the study.

**Downtown Health Plaza (DHP):** Due to the vulnerability of patients seen at DHP, protocols that propose the use of this facility should be evaluated and approved. Approval by the DHP and IRB are required prior to initiation of the study.

**Institutional Legal Counsel:** The IRB Director meets periodically with the institutional legal counsel as well as representatives of the privacy and compliance offices, IT security, and human resources to discuss research matters and apply institutional, local, state, and federal laws to research standards.

**Creative Communications:** Studies that involve the use of advertising and recruitment material must be approved by the Creative Communications department to ensure appropriate institutional branding and non-coercive appearances.

**Pharmacy:** Studies involving the use of drugs, supplements, or other biologics will be reviewed by the investigational drug services to verify the plans for safe storage, management, and dispensation of the products being studied.

**General Internal Medicine Review Committee:** Due to the vulnerability of patients seen in these clinics, protocols that propose the use of these clinics should be evaluated and approved. Approval of the committee and the IRB is required prior to study initiation.

**Office of Clinical Research:** Funded studies or those with potential billing risk to participants must be reviewed and a Medicare Coverage Analysis completed when applicable.

Oversight and Outreach: Oversight and Outreach reviews are conducted to ensure that investigators are conducting the study protocol in an ethical manner and according to institutional policies and good clinical practice guidelines. Review can be conducted at random, investigator initiated, for cause, or to investigate a potential conflict of interest. During the process of review, the monitor will also review the IRB records to ensure all regulations were followed and appropriately documented in the review process.

Office of Sponsored Programs: Studies that are supported by sponsors must negotiate a clinical trial or funding agreement with WFUHS. The director of the department, or their designee is responsible for reviewing contracts to ensure the items below are addressed.

- Medical care for research participants with a research-related injury
- Timely reporting of events/findings that could affect the safety of participants of influence the conduct of the study
- Provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to WFUHS and the timeframe with which they will be received
- Plans for disseminating findings from the research and the roles that researchers and sponsors will play in the publication or disclosure of results
- Plans to let WFUHS know of any study results that could affect the safety of former study participants once the study has ended

The committees and groups above have separate and independent review responsibilities within the institution. Representatives are notified via the eIRB software when a study or amendment is submitted and requires their respective committee's approval. A study or amendment will not be assigned for review by the IRB, no matter the review type, until all necessary ancillary approvals have been received.

The IRB also interacts with OHRP and the FDA. The IRB maintains a Federalwide Assurance and registration with OHRP for the conduct of human subjects research sponsored by the signatory agencies. The IRB is charged to abide by both federal/national law as well as other applicable laws. In general, state or local law is more conservative than federal/national law and would overrule the federal/national requirements. As such the IRB will follow the applicable law that offers the most protection for human subjects participating in studies conducted at the institution.

## **2. 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 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 such information in order 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 it is 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 to require completion of the same online CITI modules that investigators complete.

Outreach to the community includes 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 to assess effectiveness of the program and for planning of additional offerings.

## **XVII. Other Considerations**

### **1. Compliance with International Conference on Harmonization – Good Clinical Practice (E6.)**

If there is a contract or funding agreement between a research sponsor and the Covered Organization that requires ICH-GCP (E6) be followed, or if a study is funded by NIH after January 1, 2017, it is the responsibility of the PI to submit an application through eIRB indicating review of their clinical trial in compliance with ICH-GCP.

These clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable regulatory requirements. (AAHRPP Element I.1.D.; ICH-GCP 2.1) When conducting clinical trials under ICH-GCP the PI and the research team is required to be knowledgeable of and follow all requirements of this policy as well as the additional requirements detailed in the ICH-GCP (E6) Guidance including, but not limited to those described in this section. When considering applications requesting review in compliance with ICH-GCP, the IRB will be provided with the following information in the eIRB application:

- a. The Background section of the protocol will provide information on the available nonclinical and clinical information for any investigational product used that is adequate to support the proposed clinical trial. (AAHRPP Element I.1.F.; ICH-GCP 2.4)
- b. A clear, detailed protocol either through completion of protocol fields in the eIRB application and/or a complete protocol attached to the eIRB application. (AAHRPP Element I.1.F.; ICH-GCP 2.5)
- c. The PI's current curriculum vitae or other documentation evidencing qualifications. (AAHRPP Element II.2.E.; ICH-GCP 3.1.2)
- d. Attestation from the PI that:
  - i. Verification that clinical trials are scientifically sound. (AAHRPP Element I.1.F.; ICH-GCP 2.5)
  - ii. Assurance that the PI has resources necessary to protect participants including: (AAHRPP Element I-2; ICH-GCP 4.2.3)
  - iii. Adequate numbers of qualified staff.
  - iv. Adequate facilities
- e. An Assurance Document signed by the PI indicating:
  - i. Where allowed or required, that the PI may assign some or all duties for investigational articles accountability at the trial site to an appropriate pharmacist or another appropriate individual who is under the supervision of the PI. (AAHRPP Element I.7.B.; ICH-GCP 4.6.2)
  - ii. The PI, pharmacist, or other designated individual will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused products. These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial participants. The PI will maintain records that document adequately that the participants are provided the doses specified by the study and reconcile all investigational products received from the sponsor. (AAHRPP Element I.7.B.; ICH-GCP 4.6.3)

- iii. A qualified physician (or dentist, when appropriate), who is the PI or a Co-Investigator for the clinical trial, will be responsible for all clinical trial-related medical (or dental) decisions. (AAHRPP Element III.1.C.; ICH-GCP 4.3.1)
- iv. During and following a participant's participation in the clinical trial, the PI ensures that adequate medical care is provided to a participant for any [adverse events](#), including clinically significant laboratory values, related to the clinical trial. (AAHRPP Element III.1.C.; ICH-GCP 4.3.2)
- v. The PI and research team are responsible for informing participants when medical care is needed for other illnesses of which the researcher team becomes aware. (AAHRPP Element III.1.C.; ICH-GCP 4.3.2)
- vi. The PI will follow the clinical trial's randomization procedures, if any, and ensure that the code is broken only in accordance with the protocol. If the clinical trial is blinded, the PI will promptly document and explain to the Sponsor any premature unblinding. (AAHRPP Element III.1.C.; ICH-GCP 4.7)
- vii. The PI will inform the participant's primary physician about the participant's participation in the clinical trial if the participant has a primary physician and if the participant agrees to the primary physician being informed. (AAHRPP Element III.1.E.; ICH-GCP 4.3.3)
- viii. Although a participant is not obliged to give his or her reasons for withdrawing prematurely from a clinical trial, the PI will make a reasonable effort to ascertain the reason, while fully respecting the participant's rights. (AAHRPP Element III.1.E.; ICH-GCP 4.3.4)
- ix. The research team will provide all the disclosures and follow the requirements pertaining to consent covered by ICH-GCP. (AAHRPP Element III.1.F.; ICH-GCP 4.8)
- x. The PI will provide evidence of his or her qualifications through up-to-date curriculum vitae or other relevant documentation requested by the Sponsor or IRB. (AAHRPP Element III.2.A.; ICH-GCP 4.1.1)
- xi. The PI is familiar with the appropriate use of the investigational product, as described in the protocol, in the current investigator brochure, in the product information, and in other information sources provided by the Sponsor. (AAHRPP Element III.2.A.; ICH-GCP 4.1.2)
- xii. The PI will permit monitoring and auditing by the Sponsor and inspection by the appropriate regulatory authority. (AAHRPP Element III.2.A.; ICH-GCP 4.1.4)
- xiii. The PI ensures the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor. (AAHRPP Element III.2.A.; ICH-GCP 4.9.1)
- xiv. The PI maintains the clinical trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirements. (AAHRPP Element III.2.A.; ICH-GCP 4.9.4)
- xv. Essential documents are retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. (AAHRPP Element III.2.A.; ICH-GCP 4.9.5)
- xvi. The PI will maintain a list of appropriately qualified persons to whom they have delegated significant clinical trial-related duties. (AAHRPP Element III.2.B.; ICH-GCP 4.1.5)
- xvii. The PI will report all [serious adverse events](#) (SAEs) to the Sponsor except for those SAEs that the protocol or other document (e.g., Investigator's brochure) identifies as not needing immediate reporting. The PI follows regulatory requirements

- related to the reporting of unexpected serious adverse drug reactions to the regulatory authority and the IRB. (AAHRPP Element III.2.D.; ICH-GCP 4.11.1)
- xviii. The PI will report [adverse events](#) or laboratory abnormalities identified in the protocol as critical to safety evaluations to the Sponsor according to the reporting requirements and within the time periods specified by the Sponsor in the protocol. (AAHRPP Element III.2.D.; ICH-GCP 4.11.2)
  - xix. For reported deaths, the PI will supply the Sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports). (AAHRPP Element III.2.D.; ICH-GCP 4.11.3)
  - xx. The PI will provide written reports to the Sponsor, the IRB, and, where applicable, the Organization on any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants. (AAHRPP Element III.2.D.; ICH-GCP 4.10.2)
  - xxi. If the PI terminates or suspends the clinical trial without prior agreement of the Sponsor, the PI will inform the Organization, Sponsor, and the IRB. (AAHRPP Element III.2.D.; ICH-GCP 4.12.1)
  - xxii. If the IRB terminates or suspends approval of the clinical trial, the PI will promptly notify the Sponsor. (AAHRPP Element III.2.D.; ICH-GCP 4.12.3)
  - xxiii. Upon completion of the clinical trial, the PI will inform the Organization and the IRB with a summary of the trial's outcome; and the regulatory authority with any reports required. (AAHRPP Element III.2.D.; ICH-GCP 4.13)

For clinical trials conducted under ICH-GCP, PIs are responsible for following reporting requirements as described previously. In addition, the following must also be reported as New information as described previously

- a. New information that may affect adversely the safety of the participants or the conduct of the clinical trial.
- b. Any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.

When adults are unable to consent, the IRB makes the following determinations:

- a. A non-therapeutic clinical trial (i.e. a trial in which there is no anticipated direct clinical benefit to the participant) is conducted in participants who personally give consent and who sign and date the written consent document.
- b. A non-therapeutic clinical trial may be conducted in participants with consent of a legally acceptable representative provided the following conditions are fulfilled:
  - i. The objectives of the clinical trial cannot be met by means of a trial in participants who can give consent personally.
  - ii. The foreseeable risks to the participants are low.
  - iii. The negative impact on the participant's well-being is minimized and low.
  - iv. The clinical trial is not prohibited by law.
  - v. The determination of the IRB is expressly sought on the inclusion of such participants, and the determination is documented. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Participants in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

For planned emergency research, the participant or the participant's legally authorized representative is informed about the clinical trial as soon as possible and provides consent if the participant wishes to continue.

Prior to a participant's participation in the trial, the written consent document should be signed and personally dated by the participant or by the participant's legally authorized representative.

Prior to a participant's participation in the trial, the written consent document should be signed and personally dated by the person who conducted the informed consent discussion.

If a participant is unable to read or if a legally authorized representative is unable to read, an impartial witness should be present during the entire informed consent discussion.

After the written consent document and any other written information to be provided to participants, is read and explained to the participant or the participant's legally authorized representative, and after the participant or the participant's legally authorized representative has orally consented to the participant's participation in the trial and, if capable of doing so, has signed and personally dated the consent document, the witness should sign and personally date the consent document.

By signing the consent document, the witness attests that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the participant or the participant's legally authorized representative, and that consent was freely given by the participant or the participant's legally authorized representative.

Prior to participation in the trial, the participant or the participant's legally acceptable representative should receive a copy of the signed and dated written consent document and any other written information provided to the participants.

## **2. Research that is supported by the Department of Defense (DoD)**

Human subjects research that is supported or conducted by the Department of Defense (DoD) must comply with the requirements described in this section, as well as all other IRB policies and procedures as applicable.

### *Definitions*

- a. **Minimal Risk:** The definition of the minimal risk based on the phrase "ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests" will 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 will 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)
- b. **Research involving a human being as an experimental subject:** An activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction.

Research involving a human being as an experimental subject is a subset of research involving human subjects.

- c. [Prisoner](#): As defined in 45 CFR 46 subpart C, but explicitly includes military personnel in either civilian or military custody or detention.

Initial and continuing research ethics education is required for all personnel who conduct, review, approve, oversee, support, or manage human participants research. This requirement may be fulfilled by completing the WFUHS required CITI training and/or there might be specific DoD educational requirements or certification required, dependent upon the component funding 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.

For non-exempt research, the IRB will consider the scientific merit of the research and may rely on outside experts to provide this evaluation.

When research is conducted with international populations, documentation of the permission to conduct the research in that country by certification or local ethics review is required prior to IRB approval. The research will also be required to follow all local laws, regulations, customs, and practices.

The following will be reported by the IRB within 30 days to the DoD human research protection officer for DoD-supported research:

- a. Any determinations of serious or continuing non-compliance
- b. Any [suspension](#) or termination

For DoD-supported research, the PI will report the following within 30 days to the DoD human research protection officer:

- a. When significant changes to the research study are approved by the IRB.
- b. The results of the IRB continuing review.
- c. Change of reviewing IRB.

For DoD-supported research, when the IRB is notified by any federal department, agency or national organization that it is under investigation for cause involving a DoD-supported research study, the HRPO staff will notify the DoD human research protection officer within 30 days.

If research involves surveys performed on DoD personnel, the PI will submit to the DoD for review and approval after the research study is reviewed and approved by the IRB.

Any unanticipated problems involving risks to participants or others for any DoD-supported research will be reported by the IRB to the DoD human research protection officer within 30 days.

When conducting multi-site research, a formal agreement between organizations will be required to specify the roles and responsibilities of participating sites.

The IRB will consider the appointment of a research monitor required for research that involves 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.

- a. The research monitor is appointed by name and must be independent of the team conducting the research.
- b. There may be more than one research monitor (e.g. if different skills or experience are needed).
- c. 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.
- d. The IRB must communicate with research monitors to confirm their duties, authorities, and responsibilities.
- e. The duties of the research monitor are determined on the basis of specific risks or concerns about the research.
- f. 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
- g. May discuss the research study with researchers, interview human subjects, and consult with others outside of the study.
- h. Report observations and findings to the IRB or a designated official.
- i. The research monitor has the authority to:
  - i. Stop a research study in progress.
  - ii. Remove individuals from a study.
  - iii. Take any steps to protect the safety and well-being of participants until the IRB can assess

When research involves U.S. military personnel additional protections for military research participants to minimize undue influence are required:

- a. Officers are not permitted to influence the decision of their subordinates.
- b. Officers and senior non-commissioned officers may not be present at the time of recruitment.
- c. Officers and senior non-commissioned officers have a separate opportunity to participate.
- d. When recruitment involves a percentage of a unit, an independent ombudsman is present.

When research involves U.S. military personnel, the following limitations on dual compensation apply:

- a. Prohibition on an individual receiving pay of compensation for research during duty hours.
- b. An individual may be compensated for research if the participant is involved in the research when not on duty.
- c. Federal employees while on duty and non-federal persons may be compensated for blood draws for research up to \$50 for each blood draw.
- d. Non-federal persons may be compensated for research participation other than blood draws in a reasonable amount as approved by the IRB according

The IRB will determine that the disclosure for research-related injury follow the requirements of the DoD component.

If the participant meets the definition of “experimental subject,” a waiver of the consent process is prohibited unless a waiver is obtained from the Assistant Secretary of Defense for Research and Engineering.

The Assistant Secretary for Defense for Research and Engineering may waive the requirements for consent when all of the following are met:

- a. The research is necessary to advance the development of a medical product for the Military Services.
- b. The research may directly benefit the individual experimental subject.
- c. The research is conducted in compliance with all other applicable laws and regulations.

For classified research, waivers of consent are prohibited.

If the participant does not meet the definition of “experimental subject,” the IRB may waive the consent process.

Research involving pregnant women, [prisoners](#), and children are subject to the DHHS Subparts B, C, and D.

- a. For purposes of applying Subpart B, the phrase “biomedical knowledge” must be replaced with “generalizable knowledge.”
- b. 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.
- c. Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.
- d. Research involving prisoners cannot be reviewed by the expedited procedure.
- e. When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum.
- f. In addition to allowable categories of research on prisoners in Subpart C, epidemiological research is also allowable when:
  - i. The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.
  - ii. The research presents no more than minimal risk.
  - iii. The research presents no more than an inconvenience to the participant.
- g. When a participant becomes a prisoner, if the researcher asserts to the IRB that it is in the best interest of the prisoner-participant to continue to participate in the research while a prisoner, the IRB chair may determine that the prisoner-participant may continue to participate until the convened IRB can review this request to approve a change in the research study and until the organizational official and DoD Component office review the IRB’s approval to change the research study. Otherwise, the IRB chair will 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 study. The convened IRB, upon receipt of notification that a previously enrolled human participant has become a prisoner, will promptly re-review the research study to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. The IRB will consult with a subject matter expert having the expertise of a prisoner representative if the IRB reviewing the research study does not have a prisoner representative. If the prisoner-participant can

continue to consent to participate and is capable of meeting the research study 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

Research involving a detainee as a human participant is prohibited. This prohibition does not apply to research involving investigational drugs and devices when the same products would be offered to US military personnel in the same location for the same condition.

The exemption for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Research involving prisoners of war is prohibited. Prisoner of war may be defined differently across DoD components. The HRPO full board or expedited Manager will be responsible for communicating with the DoD component human subjects officer to obtain the appropriate definition when applicable to the proposed research.

If consent is to be obtained from the experimental subjects' legally authorized representative, the research must intend to benefit the individual participant. The determination that research is intended to be beneficial to the individual experimental subject must be made by the IRB.

Exception from consent in emergency medicine research is prohibited unless a waiver is obtained from the Secretary of Defense.

Records maintained that document compliance or non-compliance with DoD regulations will 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.

### **3. Compensation for Research Participants**

The general requirements for Informed Consent as outlined in 45 CFR 46.116 (OHRP Regulations) and 21 CFR 50.20 (FDA regulations) emphasize that investigators must seek legally effective informed consent under circumstances that minimize the possibility of coercion or undue influence. Thus, the issue of compensation for a subject's participation in research must be considered in evaluating the appropriateness of the informed consent process and the informed consent document for any given protocol.

The consent document should outline the amount, schedule and conditions of earning payment as follows:

*[IF COMPENSATION FOR PARTICIPATION IS AVAILABLE, list conditions, such as dollar amount per visit or payment upon study completion.]*

You will be paid \$ if you complete all the scheduled study visits. If you withdraw for any reason

from the study before completion you will be paid \$ for each complete study visit.

OR

*[Include the following for studies where compensation is more than \$50]*

To receive payment, you must provide your social security number, name and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information you can still take part in this study but you will not be paid.

OR

*[If no payment for participation is available, including the following:]*

You will receive no payment or other compensation for taking part in this study.

*[Unless no commercial development is expected to arise from the study including the following:]*

The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation or for you to share in any profits if this should occur.

Compensation for research participation is not required. However, if research subjects are to be compensated for their participation, the total amount and the schedule of payment(s) (a per visit amount), if applicable, must be included in the informed consent document. The amount of the compensation must be "reasonable", i.e. adequate to offset expenses (such as the subject's/family's time and travel) and/or appropriate to serve as a modest compensation to participate.

The IRB will evaluate the appropriateness of the proposed compensation and method of compensation as well as timing of the disbursement to assure that neither are coercive or present undue influence (21CFR 50.20) for each protocol as part of its full board and expedited reviews.

## 4. Genome Wide Association Studies

This policy outlines how investigators at the Wake Forest will submit data and materials as well as retrieve information from the Genome-Wide Association Studies (GWAS) repository database which is maintained by the National Institutes for Health (NIH).

GWAS is the study of genetic variation across the entire genome that is designed to associate genetic variations (SNPs) with traits or with the presence or absence of disease or condition. Whole genome information, when combined with clinical and other phenotype data, offers the potential for increased understanding of basic biological processes affecting human health, improvement in the prediction of disease and patient care, and ultimately the realization of the promise of personalized medicine. Competing GWAS applications must include a GWAS data sharing plan as part of the research plan (grant application) or outline why such data sharing is not appropriate.

According to the GWAS policy, local institutions are responsible for certifying that plans for the submission of genotypic and phenotypic data to GWAS meet the expectations of the GWAS policy.

### **Responsibilities of the IRB**

The IRB is responsible for reviewing the investigator's plans for data submission, as well as the adequacy of the informed consent process and documents through which the data were obtained. Because the genotype and phenotype information generated about individuals will be substantial and, in some instances, sensitive (such as data related to the presence or risk of developing particular diseases or conditions and information regarding family relationships or ancestry), the confidentiality of the data and the privacy of participants must be protected. The IRB encourages investigators submitting data to the GWAS repository to obtain a Certificate of Confidentiality from the NIH. Certificates of Confidentiality may provide an additional safeguard with regard to compelled disclosure in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level, of information that could be used to identify individual research participants.

For studies submitting data and materials to the GWAS repository, the IRB must certify that each of the following are met:

- The data submission is consistent with all applicable laws and regulations as well as institutional policies;
- The appropriate research uses of the data and the uses that are specifically excluded by the informed consent documents are delineated;
  - The identities of research participants will not be disclosed to the NIH GWAS data repository; and
  - An IRB and/or Privacy Board, as applicable, reviewed and verified that:
  - The submission of data to the NIH GWAS data repository and subsequent

sharing for research purposes are consistent with the informed consent of study participants from whom the data were obtained;

- The investigator's plan for de-identifying datasets is consistent with the standards outlined in the policy;
- It has considered the risks to individuals, their families, and groups or populations associated with data submitted to the NIH GWAS data repository; and
- The genotype and phenotype data to be submitted were collected in a manner consistent with 45 CFR Part 46.

### **Responsibilities of the Investigator**

The data submitted for inclusion in the NIH GWAS data repository will be [coded](#) and [de-identified](#) by the submitting investigator; however, the investigator may retain the key to the code that would link to specific individuals. The National Center for Biotechnology Information (NCBI) which houses the GWAS repository will never receive the code or any other information that would enable the identification of the individuals who are the source of the data.

In order to minimize risks to study participants, data submitted to the NIH GWAS data repository will be [de-identified](#) and [coded](#) using a random, unique code. Data should be [de-identified](#) according to the following criteria:

1. The identities of data subjects cannot be readily ascertained or otherwise associated with the data by the repository staff or secondary data users
2. The 18 identifiers enumerated at section 45 C.F.R. 164.514(b)(2) (the HIPAA Privacy Rule) are removed;
3. The submitting institution has no actual knowledge that the remaining information could be used alone or in combination with other information to identify the subject of the data.

### **Submission of Data Collected Prospectively**

To submit data and materials to the GWAS for prospective studies (studies in which informed consent will be obtained prospectively), investigators must provide the following information to the IRB for consideration:

- a. Documentation that data submission is consistent with applicable laws and institutional policy The appropriate research uses of the data and any specific research exclusions as outlined in the informed consent document
- b. Confirmation that the materials and data submitted to the GWAS data repository are de-identified per the HIPAA Privacy Rule regulations and at no time will the link to the identifying information, nor the actual identifying information, be disclosed to the GWAS

data repository.

- c. The informed consent document should include information regarding the data sharing. The informed consent must be clear that DNA will undergo genome-wide analysis and that genotype and phenotype will be shared for research purposes with investigators who submit proposals to the GWAS data repository. (The Informed Consent template contains suggested language for use in informed consent documents).

#### **Submission of Data Collected Previously**

To submit data and materials to the GWAS data repository for retrospective studies (studies in which informed consent was collected previously as part of a research study), investigators must provide the following information to the IRB for consideration:

- a. Documentation that data submission is consistent with applicable laws and institutional policy
- b. The appropriate research uses of the data and any specific research exclusions as outlined in the informed consent document
- c. Confirmation that the materials and data submitted to the GWAS data repository are de-identified per the HIPAA Privacy Rule regulations and at no time will the link to the identifying information, nor the actual identifying information, be disclosed to the GWAS data repository.

The IRB must review the informed consent documents which were signed by participants to confirm whether or not the initial consent under which genetic materials were obtained is consistent with the submission of data to the GWAS data repository and the sharing as outlined in the GWAS policy.

- a. The IRB may determine that the original consent is not consistent with submission of data to the GWAS data repository and may request re-consent of subjects.
- b. The IRB may determine that the original consent is not consistent with submission of data to the GWAS data repository and determine that it cannot verify that the criteria outlined in the GWAS policy have been met for submission of data to the GWAS data repository and therefore, such submission is not appropriate.
- c. The IRB **cannot** waive the requirement for informed consent for the submission of data and materials to the GWAS data repository.

#### **Investigators Prospective use of Data from the GWAS Repository**

Investigators choosing to request data from the GWAS data repository must submit an application to the IRB for determination that the research meets the qualifications for Not Human Subjects Research (NHSR). For additional information, please see the IRB policy for Exempt and NHSR.

#### **Withdrawal of Individual Consent**

The NIH GWAS data repository has developed policies with regard to removal of individual data records if consent is withdrawn. Submitting investigators and their institutions may request removal of data on individual participants from the data repository in the event that a research

participant withdraws consent. However, data that have already been distributed for approved research use will not be able to be retrieved.

## **5. Advertisements and Recruiting**

The IRB considers advertising for research study subjects to be the start of the subject selection and informed consent process. Advertising for research study subjects is defined as advertising that is intended to be seen or heard by prospective subjects to solicit their participation in a study. All research study advertisements must be reviewed and approved by the IRB prior to their use. The mode of advertisement should be communicated to the IRB, and final copies of printed and audio/visual advertisements must be submitted for review. The IRB must review and approve the final advertisement as potential research subjects will see it.

Advertisements may be reviewed through expedited procedures. All advertisements reviewed through expedited procedures will be reported to the IRB as information items at a convened meeting. Final copies of all advertising materials will be reviewed by representatives of the Creative Communications department.

All advertisements for research subjects must contain the following four elements:

- a. The institution or facility conducting the research
  1. The identification of the research facility should be in compliance with policies and procedures of the facility.
  2. The use of any logos should be in compliance with the policies and procedures associated with the use of the logos.
- b. The condition under study and/or the purpose of the research
  1. The advertisement must state that subjects are being recruited for a “Research Study.” The IRB expects the words “Research Study” to be used to describe what subjects are being recruited for.
  2. Advertising for recruitment into investigational research studies should not use terms such as “new treatment,” “new medication” or “new drug” without clearly explaining that the test article is investigational. No indication should be made that the drug or device being studied is safe or effective for the purposes being studied. Claims regarding the equivalence or superiority to other drugs or devices should also not be made when advertising a research study.

The name and phone number of the department, section, or office to contact for further information regarding the study. The advertisement should include information about eligibility criteria and the purpose of the study.

The IRB study number should appear in all advertisements. For video, the IRB number should appear in either the opening or the closing frame. For audio material, the IRB number should be given at some time during the advertisement.

The following items may be included at the investigator's or the IRB's discretion:

1. In summary form, the key criteria that will be used to determine eligibility for the study.
2. A brief list of participation benefits, if any. The benefits should not be more than what is outlined in the consent and/or protocol.

The advertisement should not state or imply a certainty of favorable outcomes as a result of participation.

No claims should be made, either explicitly or implicitly that the drug, biological, device, test, procedure, or intervention is safe or effective for the purposes under investigation.

No claims should be made, either explicitly or implicitly that the drug, biological, device, test, procedure, or intervention is known to be equivalent or superior to any other drug, biological, device, test, procedure, or intervention.

Exculpatory language should not be included in any advertisements.

Advertisements should not promise "free medical treatment" when the intent is only to say research subjects will not be charged for taking part in the investigation.

Advertisements may state that research subjects will be paid and the amount they will be paid. However, the advertisement should not emphasize the payment or the amount to be paid for participation by such means as larger or bold type.

The IRB may disallow advertisement of the exact amount a research subject will be paid if it is felt to be unduly coercive.

3. The time or other commitment required of the subjects.

**Recruitment of students, employees, or trainees**

Direct recruitment of students, employees or trainees is not generally allowed due to potentially coercive power structure with the University environment. Mass distribution of informational materials such as mass emails, flyers, or other means may be evaluated by the IRB for use in recruitment. The IRB must determine that the manner of delivery and the contents do not in any way imply that an individual's decision has any bearing on his or her relationship with instructors, employers, or mentors.

**Recruitment of patients**

It is preferable that patients are informed of opportunities to participate in research by someone they recognize as having a reason to know their medical history. "Cold calls" from strangers should generally be avoided. A letter of introduction from a direct care provider is usually an acceptable method of disseminating information regarding research opportunities to patients and can provide contact information for the study investigators. In the rare circumstances in which direct contact of patients by an investigator not involved in their care is the only practicable means of recruitment, care should be taken to construct the recruitment approach to best respect the privacy of the patients.

**Recruitment by outside researchers**

Outside researchers may not solicit at Wake Forest Baptist Medical Center without first contacting the IRB for a determination as to whether the research would engage the institution in research activity. The determination can be made by the IRB Director, IRB Chair, or designee. The IRB Director or Chair may require a University collaborator in order for the research activities to take place on the institutional campuses. Proof of approval from an external IRB will be required for outside investigators to conduct recruitment or other activities at the University. The IRB Director or Chair may determine that research activities by outside investigators are not appropriate for conduct on campuses and may disallow the conduct of these research activities on institutional premises.

**Payment of recruitment incentives**

The Institutional Review Board does not permit direct payment in cash or kind to any individual (e.g. study coordinator, house officer, nurse, pharmacist, other physician) for the recruitment of research study subjects. The Board views such payments as inappropriate and a conflict of interest. Recruitment bonuses paid directly to individuals are inappropriate, since the study is paying personnel for recruitment duties and other associated responsibilities. Recruitment bonuses may also influence referral of subjects to certain protocols, at the exclusion of other protocols, which Board views as a conflict of interest.

Wake Forest School of Medicine (WFUSM) policy does not permit individuals to receive payments or benefits in exchange for referrals. [Wake Forest School of Medicine Standards of Excellence]. Recruitment of study participants is viewed as a referral. Therefore, WFUSM policy does not permit a sponsor of a research study to directly pay (in cash or kind) any School employees.

One acceptable practice would be to pool such additional payments. These payments should be made to the School (not an individual) and deposited into a School account. These funds could then be used professional development activities such as attendance at continuing education programs or appropriate professional meetings. Distribution of pooled funds should be under

appropriate, pre-established guidelines for professional activities and not as individual incentives.

## 6. Case Reports

A Case Study or Case Report is a description of the clinical characteristics or treatment(s) provided to a single patient or a small group of patients that share a common condition, that did not involve activities defined as research in the Code of Federal Regulations (i.e. “[systematic investigation](#), including research development, testing and evaluation, designed to develop or contribute generalizable knowledge”). Innovative medical procedures or conventional treatments can be described in a case report provided that these activities do not involve research. Case reports may include more than one subject or case. Statistical analysis of the data presented in a case report must be primarily descriptive in nature, i.e. means, standard deviations and measures of central tendency are acceptable, whereas comparative statistics such as t-tests and ANOVA are not appropriate for case reports.

Because a case report is developed for medical/educational purposes, the use of protected health information (PHI) to prepare the manuscript does not require IRB review. However, the use of PHI in preparing and publishing a case report must comply with HIPAA regulations. A signed authorization should have been obtained from either the patient (or their legally authorized representative) prior to receiving clinical care. To protect the identity of the patient(s) involved, according to the HIPAA privacy rule, none of the PHI identifiers should be included in a case report.

When PHI has been collected and analyzed, the authors should take care to convert this information to a non-identifiable format. For example, date of birth should be converted to age in years, and the dates of treatment should be numbered and reported numerically. Authors should also avoid identifying individuals by inference of characteristics.

### EXAMPLE OF A CASE REPORT

A retrospective analysis is conducted of the clinical records of patients seen in the Asthma Clinic who developed H1N1 influenza between September 1, 2009 and December 31, 2009. The report gives the mean age of all the patients seen, categorizes the different courses of treatment by age range, and gives hospitalization rates and length of stay by asthma severity.

### PLEASE NOTE:

The following are characteristics of activities that ARE considered research, and thus require review and approval by the IRB before they are carried out:

- There is a plan to collect additional information that would not ordinarily be collected in the course of standard medical care for the sake of future reporting or publication.

- Records collected for the report or publications are kept separate from clinical records (i.e. for study purposes only).
- There is a plan to prospectively randomize or compare treatment to a control group.
- There is a protocol or study plan.
- Investigational drugs or devices are involved.
- The purpose of the activity is to answer a research question, rather than to provide care.
- The data are collected prospectively with the intent of future analysis and publication.
- The data are collected for deposition in a data repository or database.
- The data are extracted and analyzed from a previously collected database.

If there are questions concerning case studies and case reports, please consult with the IRB staff for more information.

## XVIII. Glossary

Adverse Event	Any negative outcome or undesirable problem that occurs during the conduct of a study, whether or not it is associated with the conduct or oversight of a research study.
Assent	The affirmative agreement of a child or individual with impaired consent capacity to participate in research.
Authorization	The granting of rights to access PHI.
Clinical trial/study	Any investigation in human subjects intended to: discover or verify clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product; identify any adverse reactions to an investigational product; and/or study absorption, distribution, metabolism, and excretion of an investigational product to determine its safety and/or efficacy.
Coded	Any 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 a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.
Continuing non-compliance	A pattern of repeated protocol deviations that indicates a deficiency in the ability or willingness of an investigator/study team to comply with Federal regulations, IRB policies, or other institutional requirements.
Corrective Action Plan	A formal written plan submitted by an investigator in response to a protocol deviation or UAP which outlines the measures that will be taken to prevent a recurrence of the deviation, problem, or event in the future and/or reduce future risks to subjects.
Covered entity	Under HIPAA, this is a health plan, a health care clearinghouse, or a health care provider who transmits any health information in electronic form in connection with a HIPAA transaction.
Data Safety Monitoring Board	An independent group of experts who ensure subject safety and study validity by meeting at defined intervals to monitor the accruing interim data of the study and make recommendations regarding the continuation of the study.
Data Use Agreement	Documents by which the covered entity can obtain satisfactory assurance that the recipient of the limited data set will use or disclose the PHI for the purposes specified in the document.
De-identified Data	A data set in which the 18 defined HIPAA identifiers have been deleted. A de-

Set	identified data set is not protected by the Privacy Rule and may be used and disclosed without restriction.
Disclosure	The release, transfer, provision of, access to, or divulging in any other manner of information outside the entity holding the information.
Emergency Use	The use of an investigational drug or biological 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.
Good Clinical Practice (GCP)	A standard established by the International Conference on Harmonization for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of clinical trial subjects are protected.
Guardian	An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.
Health Care provider	A provider of services, a provider of medical or health services, and any other person or organization who furnishes, bills, or is paid for health care in the normal course of business.
Health Plan	An individual or group plan that provides, or pays the cost of, medical care.
Health Care Clearing House	A public or private entity that either processes or facilitates the processing of health information.
Human Subject (FDA)	An individual who is or becomes a participant in research, either as a recipient of the test article or as a control.
Human Subject (HHS)	A living individual about whom data is collected through intervention or interaction or identifiable information is collected.
Identifiable private information	Information obtained from or about subjects that is individually identifiable which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public.
International Conference on Harmonization	Voluntary, international initiatives to increase coordination of the requirements for developing and marketing new drugs.
Intervention	Both physical procedures by which data are gathered and manipulations of the subject or the subject's environment that are performed for research purposes.
Investigational	A pharmaceutical form of an active ingredient or placebo being tested or used as a

product	reference in a clinical trial, including a product with marketing authorization when used for assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
Legally Authorized Representative (LAR)	an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.
Life-threatening	Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.
Limited Data Set	One in which direct identifiers have been removed, but certain potential identifiers remain as defined by the HIPAA Privacy Rule Regulations. A limited Data Set can include all elements of dates, address, and a unique identifier and must be accompanied by a Data Use Agreement.
Medical device	Any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things, surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, and orthopedic pins. Medical devices also include diagnostic aids such as reagents and test kits for in vitro diagnosis (IVD of disease and other medical conditions such as pregnancy).
Minor	As defined by NC State Law, are subjects less than 18 years of age unless emancipated, in the armed forces, or legally married.
Non-significant risk device	Device investigation is one that does not meet the definition for a significant risk study.
Parent	A child's biological or adoptive parent.
Permission	The agreement of parent(s) or guardian to the participation of their child or ward in research.
Prisoner	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, or under house arrest. [45 CFR 46.303(c)]
Protected Health Information	Individually identifiable health information that is transmitted by, or maintained in, electronic media or any other form or medium by a health care provider, a health plan or health care clearinghouse.
Protocol Deviation	Any event, action, or activity associated with the conduct or oversight of a human subject research study that fails to comply with the approved study protocol or consent; IRB Policies and procedures; Federal agency regulations; or other applicable regulatory policies governing such research, regardless of whether or not it causes harm of any kind to research subjects, increases the risk of harm, or otherwise negatively impacts their safety, rights, welfare, or privacy.
Significant Risk Device	A study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
Serious Adverse Event	An adverse event that results in: 1) death; 2) a life-threatening situation; 3) hospitalization; 4) disability or permanent damage; 5) congenital anomaly or birth defect; 6) the immediate need for medical or surgical intervention to prevent one of these outcomes.
Serious Non-Compliance	Any protocol deviation that causes harm of any kind to a research subject; adversely affects subjects' safety, rights, welfare, or privacy; or compromises the scientific integrity of the study
Severely debilitating	Diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.
Sponsor-investigator	An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than the individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.
Suspension	Some or all of the research activities must temporarily cease.
Systematic investigation	An activity that involves a prospective research plan which incorporates data collection, either quantitative or qualitative, and data analysis to answer a research question.

Termination	All research activity permanently ceases.
Test Article	Any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under these sections.
Unanticipated problem	Any event, action, or activity associated with the conduct or oversight of a human subject research study - not articulated in the study protocol or consent or expected as a consequence of the natural history of a disease under study- that causes physical, psychological, economic, or social harm to a human subject; increases the risk of harm of any kind; or otherwise compromises subject's safety, rights, welfare, or privacy. Please note that many study deviations are not unanticipated problems (UAPs) and that not all UAPs are study deviations.
Unapproved medical device	a device that is used for a purpose or condition for which the device requires, but does not have, an approved application for premarket approval under section 515 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 360(e)].
Unexpected	Not identified by nature, severity, or frequency in the investigator's brochure, sponsor protocol, or current IRB approved research protocol or informed consent document, taking into account the characteristics of the subject population being studied.
Unrelated	Any event, incident, experience, or outcome which is determined to be <b>solely</b> caused an underlying disease, disorder, or condition of the subject; or other circumstances unrelated to the subject's participation in the research.
Ward of the state	A child who is placed in the legal custody of the State or other agency, Institution, or entity, consistent with applicable Federal, State, or local law.