

University of Virginia
Standard Operating Procedures for the
Human Research Protection Program
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1 Human Research Protection Program

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

1.1 Mission

The mission of the HRPP is to:

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

The HRPP includes mechanisms to:

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

1.2 Organizational Authority

University of Virginia Human Research Protection Program operates under the authority of the Organization policy “University of Virginia Human Research Protection Program (HRPP)” adopted on July 7, 2017. As stated in that policy, the operating procedures in this document “...serve as the governing procedures for the conduct and review of all human research conducted under the auspices of the University of Virginia.” The HRPP Policy and these operating procedures are made available to all University of Virginia investigators and research staff and are posted on the HRPP website (<http://www.virginia.edu>).

1.3 Definitions

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

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

Note: The terms “subject” and “participant” are used interchangeably in this document and have the same definition throughout the materials and guidance for the University of Virginia’s HRPP program.

Research. The Common Rule defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge. Activities which meet this definition constitute research whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

For the purposes of this policy, a “**systematic investigation**” is an activity that involves a prospective study plan that incorporates data collection, either quantitative or qualitative, and data analysis to answer a study question. Investigations designed to develop or contribute to **generalizable knowledge** are those designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.

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

The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [21 CFR 50.3(c), 21 CFR 56.102(c)]

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

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

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

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

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

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

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

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

- a) **Human drugs** – The primary intended use of the product is achieved through chemical action or by being metabolized by the body. A drug is defined as a substance recognized

by an official pharmacopoeia or formulary; a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; a substance (other than food) intended to affect the structure or any function of the body; a substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.)

<http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm>

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

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm>

- c) **Biological Products** - include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.

<http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm>

- d) **Food Additives** - A food additive is defined in Section 201(s) of the FD&C Act as any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use); if such substance is not Generally Recognized As Safe (GRAS) or sanctioned prior to 1958 or otherwise excluded from the definition of food *additives*.

<http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm>

- e) **Color Additives** - A color additive is any dye, pigment or substance which when added or applied to a food, drug or cosmetic, or to the human body, is capable (alone or through reactions with other substances) of imparting color. Color additives for use in food,

drugs, and cosmetics require premarket approval. Color additives for use in or on a medical device are subject to premarket approval, if the color additive comes in direct contact with the body for a significant period of time. <http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm>

- f) **Foods** - Foods include dietary supplements that bear a nutrient content claim or a health claim.
- g) **Infant Formulas** – Infant formulas are liquid foods intended for infants which substitute for mother’s milk.
- h) **Electronic Products** - The FDA regulates certain classes of electronic products including radiation-emitting electronic products such as microwaves and x-rays.

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

1.4 Ethical Principles

The University of Virginia is committed to conducting research with the highest regard for the welfare of human subjects. With the exception of international research, where consideration of alternative ethical principles may apply (see Section 25), the University of Virginia upholds and adheres to the principles of *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research* by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (1979). These principles are:

- 1) **Respect for Persons**, which involves obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.
- 2) **Beneficence**, which involves ensuring that possible benefits are maximized and possible risks are minimized to all human subjects.
- 3) **Justice**, which involves the equitable selection of subjects.

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

1.5 Regulatory Compliance

The HRPP is responsible for ensuring compliance with federal regulations, state law and organizational policies. All human subjects research at the University of Virginia is conducted in accordance with the policy and regulations found in the Common Rule and 21 CFR 50 and 56. The actions of the University of Virginia will also conform to all other applicable federal, state,

and local laws and regulations such as those specific to the Department of Defense (DoD), Department of Education (DoE), US Department of the Army, Department of Transportation National Highway Traffic Safety Administration, Department of Justice (DoJ), and the Family Educational Rights and Privacy Act (FERPA).

Research supported by the Department of Defense (DoD) is reviewed and conducted in compliance with part 219 of title 32 CFR, part 980 of title 10 USC, applicable parts of title 21 CFR (50, 56, 312, 600, 812), DoD Instruction 3216.02, DoD Directive 3210.07, and applicable additional requirements from respective DoD component(s).

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

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

1.6 International Council on Harmonization-Good Clinical Practice (ICH-GCP)

The University of Virginia voluntarily applies the International Council on Harmonization (“ICH”) Good Clinical Practices (“GCP”) Guidelines (sometimes referred to as “ICH-GCP” or “E6”) to human subject research in a clinical trial conducted under a UVA IRB only to the extent that they are compatible with FDA and DHHS regulations.

The following procedures will be followed:

- Manufacturing, handling, and storage of investigational articles will be conducted in accordance with applicable good manufacturing practice.
- The available nonclinical and clinical information on an investigational product is adequate to support the proposed clinical trial.
- Where allowed or required, the researcher may assign some or all duties for investigational articles accountability at the trial sites to an appropriate pharmacist or another appropriate individual who is under the supervision of the researcher.
- The researcher, pharmacist, or other designated individual will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused products. These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial subjects.
- Researchers should maintain records that document adequately that the subjects are provided the doses specified by the protocol and reconcile all investigational products received from the sponsor.

1.7 Federalwide Assurance (FWA)

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

The University of Virginia has an OHRP-approved Federalwide Assurance [00006183] and has designated three IRB(s) to review all human research plans.

- IRB-HSR:IRB#1 Registration # 00000447
- IRB-SBS:IRB#2 Registration # 00000448
- IRB-HSR:IRB#3 Registration # 00010459

In its FWA, the University of Virginia has opted to voluntarily apply the Common Rule (i.e., Subpart A) to all of its human subject research including all non-federally funded research. Subparts B, C, and D of 45 CFR 46 are applied to all research regardless of funding with the exception of Subpart B which will not be applied to social, behavioral, educational and non-therapeutic medical research.

1.8 Research Under the Auspices of the Organization

Research under the auspices of the organization includes research conducted at this organization, conducted by or under the direction of any employee or agent of this organization (including students) in connection with his or her organizational responsibilities, conducted by or under the direction of any employee or agent of this organization using any property or facility of this organization, or involving the use of this organization's non-public information to identify, contact, or study human subjects.

Employee or Agent. For the purposes of this document, *employees or agents* refers to individuals who: (1) act on behalf of the organization; (2) exercise organizational authority or responsibility; or (3) perform organizationally designated activities. "Employees and agents" can include staff, students, contractors, and volunteers, among others, regardless of whether the individual is receiving compensation.

Engagement. The Department of Health and Human Services (DHHS) regulations [[45 CFR 46.103\[a\]](#)] require that an institution "engaged" in human subject research conducted or supported by a Federal Department or Agency provide the Office for Human Research Protection (OHRP) with a satisfactory assurance of compliance with the DHHS regulations, unless the research is exempt under [45 CFR 46.101\(b\)](#). *"In general, an institution is considered engaged in a particular non-exempt human subjects research project when its*

employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research.” In general, institutions that receive an award through a grant, contract, or cooperative agreement directly from DHHS for the non-exempt human subjects research (i.e. awardee institutions), are also considered engaged in research even where all activities involving human subjects are carried out by employees or agents of another institution.

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

An experienced member of the IRB staff in consultation with the IRB Chair, Vice Chair, and/or legal counsel as needed, will determine whether the University of Virginia is engaged in a particular research study. Investigators and other institutions may not independently determine University of Virginia engagement.

When the University of Virginia is engaged in research, the Institutional Official may choose to enter into an agreement to cede review to an external IRB.

For additional information on determining engagement please refer to Guidance on Engagement on Institutions in Human Subjects Research, <http://www.hhs.gov/ohrp/policy/engage08.html>

1.9 Written policies and procedures

The University of Virginia Standard Operating Policies and Procedures for Human Research Protection detail the policies and regulations governing research with human subjects and the requirements for submitting research proposals for review by the University of Virginia IRB. This is not a static document. The policies and procedures are annually reviewed and revised by the IRB Directors and reviewed by the IRB Chairs prior to approval by the Institutional Official.

The Institutional Official will keep the Organization research community apprised of new information that may affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues on its website and through electronic mailing lists. The policies and procedures will be available on the University of Virginia HRPP website. Changes to the policies and procedures are communicated to investigators and research staff, and IRB members and IRB staff by way of emails and postings on the HRPP and IRB websites.

1.10 University of Virginia HRPP Structure

The HRPP consists of various individuals and committees including but not limited to:

- The Institutional Official,
- The HRPP Director,
- The IRB Directors, Staff, and Committee Members,
- The Institutional Biosafety Committee (IBC),
- Human Investigations involving Radiology Exposure (HIRE) Committee,
- The Radioactive Drug Research Committee (RDRC),
- University Conflict of Interest Committee (UCOI),
- School of Medicine Conflict of Interest Committee (SOM COI),
- Office of Sponsored Programs (OSP),
- School of Medicine Grants and Contracts office (SOM-OCG),
- School of Medicine Clinical Trials office (SOM-CTO),
- General Counsel,
- Office of Environmental Health and Safety (EHS),
- Investigational Drug Services (IDS)
- Information Security (InfoSec),
- Group on Research in Medical Education (GRIME) and Graduate Medical Education Committee (GMEC), and
- Researchers and support staff.

The objective of this system is to assist the organization in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

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

1.10.1 Institutional Official

The ultimate responsibility of the HRPP resides with the **Institutional Official (IO)** of the program. The IO is legally authorized to represent the University of Virginia. The IO is the signatory of the FWA and assumes the obligations of the FWA. At the University of Virginia, the Vice President for Research serves as the IO. The IO is responsible for ensuring that the University of Virginia HRPP and IRBs have the resources and support necessary to comply with all organizational policies, laws, and regulations that govern human subject research. Such resources include, but are not limited to:

- Staffing commensurate with the size and complexity of the research program;
- Appropriate office space, equipment, materials, and technology;
- Resources for the production, maintenance, and secure storage of HRPP and IRB records;
- Resources for auditing and other compliance activities and investigation of non-compliance;
- Access to legal counsel; and
- Supporting educational opportunities related to human research protections for IRB members, relevant administrative staff, and all members of the research team.
- Support for evaluation of Conflict of Interest;
- Support for Community Outreach;
- Support for an organizational culture that fosters and maintains the ethical conduct of research involving human subjects and adherences to regulations and organizational policies; and,
- Support for the oversight of the conduct of research by all University of Virginia investigators.

The IO must complete the OHRP Human Subject Assurance Training, the University of Virginia's required CITI Training, and any other appropriate training on human research protections. The HRPP Director will provide on-going continuing education for the IO concerning human research protections.

The designated IO is made known to employees of the organization and is accessible by phone, email, in person or other methods of communication.

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

1.10.2 Director of the HRPP

The HRPP Director is selected by and reports to the Institutional Official (IO).

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

The HRPP Director responsible for:

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

- Oversight of the Institutional Review Board for Health Sciences Research (IRB-HSR) and the Institutional Review Board for the Social and Behavioral Sciences (IRB-SBS);
- Assuring the IRB members are appropriately knowledgeable to review research in accordance with ethical standards and applicable regulations;
- Assuring that all investigators are appropriately knowledgeable to conduct research in accordance with ethical standards and applicable regulations;
- Oversight of the development and implementation of an educational plan for IRB members, staff and investigators;
- Oversight of the budgetary processes of the University of Virginia's HRPP;
- Completing the OHRP Human Subject Assurance Training, the required CITI training and any other appropriate training on human research protections.
- Developing, managing and evaluating policies and procedures that ensure compliance with all state, and federal regulations governing research. This includes monitoring changes in regulations and policies that relate to human research protection and overseeing the administration of the IRB.
- Assisting investigators in their efforts to carry out Organization's research mission.
- Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program.
- Serving as the primary contact at the University of Virginia for the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services, the Food & Drug Administration (FDA) and other federal regulatory agencies.
- Responding to questions regarding the protection of human subjects.
- Working closely with the IRB Directors and Chairs on the development of policy and procedures, as well as organizing and documenting the review process.
- Developing and monitoring timely completion of training requirements for Conflict of Interest (COI), Embryonic Stem Cell Research Oversight (ESCRO), and Responsible Conduct of Research (RCR) as required and as appropriate for subcommittee members, investigators and research staff;
- Advising the IO on key matters regarding research at the University of Virginia.

The HRPP Director has access to the IO for any concerns or issues related to the HRPP.

1.10.3 HRPP Staff

In addition to the leadership structure described above, other HRPP staff members include IRB Directors, Associate and Assistant Directors, IRB Compliance Coordinators, a Compliance Content Specialist, Post Approval Monitors, IRB Educators and Office Administrators. The HRPP and IRB staff for the University of Virginia must comply with all ethical standards and practices.

The duties and responsibilities for all staff are found in their respective job descriptions, and their performance is evaluated on an annual basis. The University of Virginia HRPP staff report to the HRPP Director who has responsibilities for its operations.

The IRB Directors have responsibility for implementing the organization's HRPP policies and procedures under the direction of the HRPP Director and guidance of University General Counsel. The IRB Directors also oversee the day-to day operations of the IRB offices.

1.10.4 Institutional Review Board (IRB)

The University of Virginia has three on site IRBs, appointed by the Institutional Official (IO). The IRB prospectively reviews and makes decisions concerning all human research conducted at University of Virginia facilities, by its employees or agents, or under its auspices unless another IRB has been designated to do so. The IRB is responsible for the protection of rights and welfare of human research subjects at the University of Virginia, through review and oversight of safe and ethical research. It discharges this duty by complying with the requirements of federal and state regulations, the FWA, and organizational policies. (See Section 4 for a detailed discussion of the IRB.)

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

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

1.10.5 General Counsel's Office

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

1.10.6 Department Chairs and/or Organizational Leaders and their Designees

Department Chairs and organizational leaders and their designees are responsible for ensuring that the investigator is qualified by training and experience to conduct the proposed research. For each research study submitted to the University of Virginia IRB for approval, the department chair, leaders, faculty advisor or designee must certify that s/he accepts responsibility for supporting adherence to the federal and state regulations and organizational policies governing the protection of human subjects of research, including applicable organizational credentialing requirements. Department chairs/leaders/faculty

advisors/designees are responsible for assuring that investigators have the resources required to conduct the research in a way that will protect the right and welfare of participants. Such resources include but are not necessarily limited to personnel, space, equipment and time.

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

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

1.10.7 The Investigator

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

1.10.8 Other Related Units

1.10.8.1 Sponsored Programs Administration

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

Sponsored Programs Administration ensures that required AAHRPP language (see Section 20.2) is included in contracts as appropriate. Sponsored Programs Administration has access to the relevant documents to confirm that the contract and the consent documents are consistent in terms of who pays in case of injury. Sponsored Programs Administration and the IRB office

coordinate efforts to ensure that all applicable individuals have filed appropriate COI disclosures to meet investigator COI policies.

When the grant or contract agreement includes human research activities that will be conducted by investigators who are not employees or agents of the University of Virginia, a subcontract is executed between the University of Virginia and the collaborating institution. The subcontract includes the requirement for the collaborating institution to assure compliance with federal regulations for the protection of human subjects in research and to provide documentation of current and ongoing IRB approval. The collaborating institution must also ensure that key personnel involved in human subject research are in compliance with the NIH policy on education in the protection of human research subjects and provide documentation of education of key personnel to the University of Virginia. . *This requirement is waived if Sub-recipient's FCOI Policy is PHS compliant.* If the contrary, then the Sub-recipient is required to adhere to UVA's FCOI Policy, is provided with the Financial Disclosure Form, and is asked to submit the form to VPR Office for review and COI determination.

1.10.8.2. University of Virginia Investigational Drug Service (UVA IDS)

A pharmacist from the University of Virginia Investigational Drug Service (UVA IDS) serves on the IRB, allowing the IDS to have complete information about all IRB approved research that takes place at the University of Virginia and under its jurisdiction. The Pharmacist member assures that information about all studies involving drugs used in research is shared with both the Pharmacy Staff as appropriate and that the University of Virginia Hospital Pharmacy and Therapeutics Committee is made aware of IRB approved research involving drugs.

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

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

1.10.8.3 University of Virginia Cancer Center Protocol Review Committee (PRC)

The Protocol Review Committee (PRC) serves as the UVA Protocol Review and Monitoring System as required by the National Cancer Institute (NCI). The PRC is charged with providing institutional peer-review of the scientific merit of all cancer related clinical research protocols. The primary goal of the PRC is to ensure that cancer-related studies involving human subjects conducted at the UVA Cancer Center are:

- Scientifically and statistically sound;
- Appropriately designed;
- Feasible for completion; and

- In compliance with NIH guidelines for human studies.

As part of the review process, the PRC:

- review and approve protocol-specific data and safety monitoring plans on cancer-related trials prior to protocol review by the IRB and
- determine if a protocol competes with existing or pending protocols for a particular subject pool. The PRC will not approve protocols that directly compete with an open or pending institutional or NCI-sponsored trial.

1.10.8.4 University of Virginia Neonatal ICU Protocol Review Committee

The Neonatal ICU Protocol Review Committee serves as the scientific review committee for all research that is conducted in the UVA Neonatal ICU. The primary goal of the NICU clinical trials research scientific review is to ensure NICU studies are performed safely, accounting for unique characteristics of preterm and full term newborns, is feasible, family friendly and the consent form accurately reflects the protocol for the family or person giving consent.

1.10.9 Relationship Among Components

The UVA Research Steering Committee will meet to ensure a dialogue is maintained between the various research compliance entities at the University. Membership is comprised of the following with the Senior Associate Vice President for Research serving as chair:

1. Office of the Vice President for Research: Senior Associate Vice President for Research
2. Institutional Review Boards: IRB Directors and Education Director
3. School of Medicine Clinical Trials Office: Director
4. Office of the General Counsel: Associate General Counsel
5. School of Medicine Office of Grants and Contracts Director; Assistant Dean for Research Administration
6. Office of Sponsored Programs: Assistant Director of Contracts
7. Office of Sponsored Programs: Assistant Vice President for Research

The committee will act in an advisory capacity to the Senior Associate Vice President for Research monitoring the effectiveness of existing compliance programs, developing new or revised policies as changes in requirements occur, and disseminating updated compliance information to the research community. The committee may consult other University personnel with expertise in critical areas as needed.

1.10.10 Study-Specific Coordination

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

- Clinical Engineering (new medical devices in health system)
- Conflict of Interest Committees (University and School of Medicine)
- Embryonic Stem Cell Research Oversight (ESCRO) Committee
- Graduate Medical Education Committee (GMEC)
- Group on Research in Medical Education (GRIME) Committee
- Human Investigations Involving Radiology Exposure (HIRE) Committee
- Institutional Biosafety Committee (IBC)
- Investigational Drug Services (IDS)
- Information Security (InfoSec) (data security approval)
- Permissions from internal or external research locations
- Permissions from internal or external offices or sites providing archived data
- Radioactive Drug Research Committee (RDRC)
- Scientific & Scholarly Review Committees (e.g., Cancer Center Protocol Review Committee (CC PRC), Neonatal ICU Protocol Review Committee)

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

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

1.11 Multi-Site Research Projects and IRB Reliance Agreements

UVA researchers are often engaged in non-exempt human subject research that may involve collaborators and/or human subjects at other institutions. In accordance with 45CFR46.114, a UVA IRB may serve as the IRB of Record only for the UVA site, UVA may rely upon the review of a qualified non-UVA IRB or a UVA IRB may serve as the IRB of Record for all sites involved in the multi-site research study. Reliance on another IRB is accomplished through the use of an IRB Authorization/Reliance Agreement. The scope of the Reliance Agreement may be limited to a specific protocol on a case-by-case basis or to any group of protocols agreed upon by both parties.

A signed IRB Reliance Agreement must be in place before a University of Virginia IRB will serve as the IRB of Record for another institution or rely on the review of a non-UVA IRB.

Information regarding IRB Reliance Agreements may be found below. Information regarding the protocol submission process for a protocol that will be overseen by a non- UVA IRB may be found in section 9.

Definitions

IRB of Record: A reviewing IRB that assumes IRB responsibilities for another organization. May also be called the Central IRB (CIRB) or Single IRB (sIRB).

IRB Reliance Agreement: A formal, written agreement in which the reviewing IRB agrees to serve as the IRB of Record for a Relying Organization.

Relying Institution: A relying Institution is the institution that has entered into an IRB Reliance Agreement with another institution's IRB to serve as the IRB of Record.

Non-Exempt Human Subject Research- any human subject research that does not meet the Exempt criteria in 45CFR46.

Engagement of Organizations in Non-Exempt Human Subject Research: An organization is considered engaged in human research when its employees or agents, for the purposes the research project obtain 1) data about the subjects of the research through intervention or interaction with them; 2) identifiable private information about the subjects of the research; 3) informed consent of human subjects for the research; OR 4) a direct federal award to conduct human subject research, even when all activities involving human subjects are carried out by subcontractors (i.e. employees or agents of another organization). HHS Guidance: [Engagement in Human Subjects Research](#)

1.11.1 UVA engaged in only a part of a Multi-Site Research Project

When the University of Virginia is engaged in only part of a cooperative research project, UVA may rely on a non-UVA IRB for the part of the study being conducted at UVA. If the study will be reviewed by a UVA IRB, the UVA IRB only needs to approve the part(s) of the research in which the University of Virginia investigator is engaged. For example, if the University of Virginia is operating the statistical center for a multi-site trial that receives identifiable private information from multiple other institutions, the UVA IRB reviews and approves the research

activities related to the receipt and processing of the identifiable private information by the statistical center.

1.11.2 Each research site obtains IRB Approval from their IRB

It is the policy of the University of Virginia to assure that all facilities participating in a study involving human subjects receive adequate documentation about the study in order to protect the interests of study participants. Before a study can begin, it must be approved by the IRB of each participating site. The lead Principal Investigator must identify all institutions participating in the research, the responsible IRB(s), and the procedures for dissemination or collection of study information (IRB initial and continuing approvals, relevant reports of unanticipated problems, study modifications, and interim reports) between all participating institutions.

Prior to signing of sub contracts with each research site the Office of Sponsored Programs/ School of Medicine Office of Grants and Contracts will obtain the IRB approval from each site.

1.11.3 UVA Relies on a non- UVA IRB as the IRB of Record

The decision for UVA to rely on a non- UVA IRB is made on a case by case basis. The decision will include such factors as:

- Risk level of the study
- Qualifications of proposed IRB of Record
- Location of subject enrollment
- Requirement to rely on a single IRB from a funding source /sponsor
- Requirements of federal regulations or policies of federal agencies.

UVA has joined SMART IRB and encourages the use of the SMART IRB Reliance Agreement template and SOP's when possible.

1.11.4 UVA IRB serves as IRB of Record for non-UVA Sites

Requests for a new reliance agreement to allow another institution or independent investigator to rely on the UVA IRB for IRB review are considered on a case-by-case basis. The Researcher requesting the reliance agreement must submit a request for an IRB reliance agreement _ to the IRB.

The requests to add relying sites will be handled as modifications. The modification to add a relying site will not take place until the UVA IRB approves the main protocol, consent and other relevant study documents for non-exempt studies.

The UVA IRB follows the same criteria for consideration of a modification meeting the criteria of expedited or full board review. The addition of a relying site is considered an expedited modification so long as there are no content revisions to the document(s) that would be greater

than minimal risks and therefore require the modification to add a relying site go before a convened IRB.

The UVA IRB will review the relying site local content revisions to the consent document and ensure that no changes have been made outside of the applicable sections outlined in the request form. Any additional revisions required for a particular relying site, will be outlined specifically in the relying site request form.

Once review is complete and the relying site is added to the protocol via a modification, the UVA study team will notify the relying sites of all determinations and communications from the UVA IRB. This includes those decisions for initial review, continuing review, modifications, and reportable events.

The UVA IRB will make available upon request, relevant IRB minutes. In addition, the Relying institutions are provided with the website links for the UVA IRB membership rosters, and standard operating procedures.

All applicable policies governing research at UVA are available via the UVA HRPP website as well as the UVA IRB website. HRPP staff are noted on the website pages including contact information.

UVA researchers are made aware of significant policy changes via a site wide email from the IRB offices. Should a policy change directly affect specific studies (e.g. COI management plan), the PI and study team are emailed with information and guidance on how to submit revisions if applicable. The UVA study teams are required to communicate relevant information directly to outside study teams.

1.11.5 UVA PI serves as Overall PI or UVA serves as the Data Coordinating Center

If a UVA investigator serves as the overall PI they or the Data Coordinating Center is responsible for:

- documenting how the conduct of the research plan and the protection of human subjects will be communicated to and among the other participating facilities engaged in the research study.
- serving as the liaison with regulatory and funding agencies, with other participating facilities, and for all aspects of internal review and oversight procedures.
- ensuring that all participating facilities obtain review and approval from their IRB of record and adopt all research plan modifications in a timely fashion.

- ensuring that the research study is reviewed and approved by any other appropriate committees at the coordinating facility and at the participating facilities prior to enrollment of participants.

The University of Virginia investigator must follow these procedures when University of Virginia is the coordinating facility or overall PI:

- During the initial IRB submission of the multi-site study, the investigator indicates in writing on the application form or in an application letter that the University of Virginia PI is the overall PI for all sites in the study and/or is the coordinating facility of a multi-site study.
- For health sciences research, the School of Medicine Clinical Trials office will verify the items noted below prior to the initial IRB review. The IRB will not open the protocol to enrollment until it has received verification from the SOM CTO.
 - Method for assuring all participating facilities have the most current version of the research plan
 - Method for confirming that all modifications to the research plan are communicated to participating sites
 - Method for communicating to participating facilities any serious adverse events and unanticipated problems involving risks to subjects or others
 - Method of communicating regularly with participating sites about study events
 - When appropriate, the plan for monitoring the conduct of the research at participating facilities
 - Method for communicating interim analyses, including data safety reviews, to participating facilities, as applicable
 - In addition, throughout the course of any federally funded study verify the investigator has the appropriate IRB approvals on file from each site and verify the FWA for each site is current.
- The IRB will verify the items noted below prior to approval is granted:
 - Name of each participating facility
 - Confirmation that each participating facility has an active FWA (including FWA number and expiration date) for all federally funded studies
 - Contact name and information for investigator(s) at each participating facility
 - Contact name and information for IRB of record at each participating facility with the IRB/ethics committee approval
- The UVA Office of Sponsored Programs will verify the items noted below before a contract is signed.

- If applicable: IRB approval from local in country IRB/Ethics Committee for international research for each site
- IRB approval from IRB of Record for each site
- The investigator will:
 - maintain documentation of all correspondence between participating sites and the IRB of Record.
 - maintain a copy of the IRB approval from all sites prior to enrollment of subjects at a site

2 Quality Assurance

University of Virginia performs Quality Assurance and Improvement activities for the purposes of monitoring the safety of ongoing studies and measuring and improving human research protection effectiveness, quality, and compliance with organizational policies and procedures and applicable federal, state, and local laws.

2.1 External Monitoring, Audit, and Inspection Reports

All reports from external monitors, auditors, or inspectors must be submitted by investigators to the IRB for review. The IRB Chair or designee will review such reports in order to monitor for issues that could impact the rights or welfare of human subjects and for issues indicative of possible serious or continuing non-compliance. If such issues are identified, the report will be forwarded to the convened IRB to determine what additional actions are necessary.

2.2 Investigator Compliance Reviews

The HRPP Post Approval Monitoring and Education (PAM&ED) program is responsible for conducting post-approval directed (“for cause”) audits and periodic (not “for cause”) compliance reviews of investigator research plans. Additionally, the PAM office may appoint a subcommittee for the purpose of conducting a for-cause or not for-cause compliance review of one or more research plans under its jurisdiction. The subcommittee may be composed of PAM&ED and IRB staff, IRB members from within, or individuals from and outside of the organization.

Compliance reviews are conducted to assess investigator compliance with federal, state, and local law, and University of Virginia policies, and to identify areas for improvement, and to provide recommendations based on existing policies and procedures. The results of compliance reviews will be reported to the IRB Directors, the IRB, and the investigator. Any non-compliance will be handled according to the procedures in Section 16.

If it is identified that subjects in a research project have been exposed to unexpected

serious harm, the reviewer will promptly report such findings to the Institutional Official and the IRB Director/Chair for immediate action.

If issues are identified that indicate possible misconduct in research, the procedures in the University of Virginia Policy on Research Misconduct will be initiated.

PAM compliance reviews may include:

- a) Examining investigator-held research records;
- b) Confirming adherence to data and safety monitoring plans;
- c) Reviewing advertisements and other recruiting materials;
- d) Verifying that the researchers have not deviated from the approved, research protocol;
- e) Confirming that documents being used by the research team align with the most recently approved IRB protocol;
- f) Verifying accurate completion of consent documents and matching subject enrollment numbers with completed consents;
- g) Determine that the investigator has followed the subject selection criteria. Under special circumstances, observing research sites where research involving human research subjects and/or the informed consent process is being conducted;
- h) Monitoring and responding to the research subject hotline;
- i) Conducting other monitoring or auditing activities as deemed appropriate by the IRB;
- j) Formulating education programs for researchers as needed through the Ed program.

2.3 IRB Compliance Reviews

The HRPP program, with, or without, the assistance of an outside organization, will periodically review the activities of the IRB to assess compliance with regulatory requirements and to identify areas for improvement; this will include a review of IRB records at least annually.

Review activities by the IRB may include:

- a) Review of the IRB minutes to determine that adequate documentation of the meeting discussion has occurred. This review will include assessing the documentation surrounding the discussion for protections of vulnerable populations as well as risk/benefit ratio and consent issues that are included in the criteria for approval;
- b) Review of the IRB minutes to assure that quorum was met and maintained;
- c) Review of IRB documentation, including IRB minutes, to assess whether privacy provisions, according to HIPAA, have been adequately reviewed, discussed and documented;
- d) Evaluating the continuing review discussions to assure they are substantive and meaningful and that no lapse has occurred since the previous IRB review;
- e) Reviewing IRB files to assure retention of appropriate documentation and consistent organization of the IRB file according to current policies and procedures;
- f) Reviewing the IRB database to assure all required fields are completed accurately;

- k) Verifying IRB approvals for collaborating institutions or external performance sites;
- l) Reviewing the appropriate metrics (for example, time from submission to first review) to evaluate the quality, efficiency, and effectiveness of the IRB review process;
- m) Reviewing the workload of IRB staff to evaluate appropriate staffing level; and
- n) Other monitoring or auditing activities deemed appropriate.

Review activities of IRB files by PAM include:

- a) Periodic reviews of IRB files to assure consistent organization of the IRB file according to current policies and procedures.

The IRB Directors and IRB Chairs will review the results of IRB compliance reviews with the Institutional Official. If any deficiencies are noted in the review, a corrective action plan will be developed by the Director and Chair and approved by the Institutional Official. The Director will have responsibility for implementing the corrective action plan, the results of which will be evaluated by the Institutional Official.

2.4 HRPP Quality Assessment and Improvement

Annually, a meeting is held by the HRPP Quality Assessment and Improvement Committee (QuAiC) comprised of the HRPP Director IRB Directors and Chairs, IO, PAM Compliance Monitors, and IRB Education Coordinator in which a quality improvement plan is put into place, to be carried out by an individual or committee named by the Institutional Official that assesses compliance and achieving targeted levels of quality, efficiency, and effectiveness of the HRPP (e.g., continuous investigator training; use of IRB-approved consent forms, turn-around time of exemption determinations, etc.). The plan will, at a minimum contain:

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

Results of the plan report is reviewed by the QuAiC HRPP in order to identify trends and to determine if systemic changes are required to prevent re-occurrence. If so, the QuAiC will collaborate in the development of a corrective action plan, its implementation, and evaluation of its effectiveness.

The IRB Directors are responsible for tracking internal metrics that are informative in considering IRB and Investigator efficiency such as the amount of time from receipt of a submission through pre-review, and final approval and the amount of time it takes investigators to develop and submit responses to pre-review and IRB requirements. Metrics reports will be provided to the IO and IRB Chairs once a year.

Annually, QuAiC, in collaboration with other relevant parties, will define Quality Improvement goals for the year. The targeted issues, goals, and means to measure progress are documented in a written QA/QI plan. In order to evaluate whether the defined goals are being achieved, PAM HRPP Compliance Coordinators collect, record, and provide a written report to the IO for tracking purposes. At the end of each year, QuAiC evaluates whether the respective goals were achieved and adjusts the affected processes to correct any deficiencies.

3 Education & Training

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

Recognizing that a vital component of a comprehensive human research protection program is an education program, University of Virginia is committed to providing training and an on-going educational process for IRB members and the staff of the IRB and HRPP Office, related to ethical concerns and regulatory and organizational requirements for the protection of human subjects.

Orientation

New IRB members, including alternate members will meet with the IRB Chair, IRB Staff or Director of the HRPP Office for an informal orientation session. At the session, the federal regulations will be reviewed and an orientation to IRB processes and on-line materials will be given. Online resources include, but are not limited to:

- Belmont Report;
- University of Virginia HRPP Standard Operating Procedures;
- Federal regulations relevant to the IRB;
- Tools used by IRB reviewers (checklists etc.).

Also, the new member will be given an Institutional Review Board Member Handbook .

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

Initial Education

IRB members and HRPP/IRB staff will complete the required modules in the CITI Course in the Protection of Human Research Subjects (biomedical or social behavioral track, as applicable), including the IRB Member Module - "What Every New IRB Member Needs to Know" and the module on Conflicts of Interest. Community members are expected to review the "I Have Agreed to be an IRB Community Member. Now What?" module as well.

Continuing Education

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

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

- In-service training at IRB meetings;

- Conference attendance;
- Copies of appropriate publications;
- Identification and dissemination by the Director of new information that might affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues to IRB members via email, mail, or during IRB meetings; and
- Unlimited access to the IRB Office resource library.

IRB members and HRPP and IRB staff are also required to complete CITI training every 3 years as part of the University of Virginia continuing education requirements.

The activities for continuing education vary on a yearly basis depending on operating budget and areas of need, as determined by the IRB Directors. The IRB Directors determine which continuing education activities are mandatory for IRB members and staff in a given year. The IRB Directors or designees track whether each individual has satisfied the requirements. IRB members who have not fulfilled their continuing education requirements will not be assigned as primary or secondary reviewer until they are fulfilled. Continuing failure to complete training may result in the individual being removed or not renewed as an IRB member. Fulfillment of training requirements is included as part of the evaluation of the performance of IRB members/alternates.

Members and staff who are unable to attend education sessions will be provided with the opportunity to make-up any training that they missed. If a make-up session is not possible (e.g., a webinar or conference), then an equivalent educational opportunity will be offered at the discretion of the Director.

The Institutional Official (IO) will provide support to send as many members of the IRB as possible to attend the annual PRIM&R conference, the Virginia IRB Consortium Conference or regional conferences on human research protections.

3.2 Training / Ongoing Education of Investigators and Research Team

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

3.2.1 Initial Education

Investigators, key personnel, and other members of the research team must complete University of Virginia required core modules in the CITI Course in the Protection of Human Research Subjects including the module on Conflicts of Interest. Evidence of current training (date of completion within 3 years of application date) for each member of the research team

must be included in every new research study application and application for continuing review.

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

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

Waiver of Initial Education

If individuals can provide documentation verifying that they have successfully completed human subject research training equivalent to that required by the University of Virginia, they may request a waiver of the requirement for Initial Education. IRB staff will review the documentation and determine if it satisfies organizational standards. However, all investigators or members of their research team must complete the requirements of Continuing Education as reviewed below.

3.2.2 Continuing Education and Recertification

Investigators, key personnel, and other members of the research team must meet the University of Virginia continuing education requirement every [three (3)] years after certification of Initial Education for as long as they are involved in human subject research. There is no exception to this requirement. Acceptable training includes attendance at approved PRIM&R, OHRP, or FDA seminars and conferences, attendance at HRPP Human Subject Research Presentations, or review of appropriate refresher modules at the CITI web-based training site. Other training may be acceptable. In these cases the investigator should check with the IRB Office for a determination.

Individuals must submit to the IRB office evidence of continuing education prior to the expiration of their training certification. New research plans and applications for continuing review will not be accepted from investigators who have not submitted satisfactory evidence of continuing education.

Investigators who are also IRB Chair, IRB members, or IRB Office staff will satisfy the training requirements for IRB members and staff described in this policy under Section 3.1.

4 Institutional Review Board

The University of Virginia has established Institutional Review Boards (IRBs) to ensure the protection of human subjects in research conducted under the auspices of the University of Virginia. All non-exempt human subject research conducted under the auspices of the University of Virginia must be reviewed and approved by a University of Virginia IRB or another designated IRB prior to the initiation of the research unless it has been determined that the University of Virginia is not engaged in the research (See Section 1.11.1).

4.1 IRB Authority

The IRB derives its authority from University of Virginia policy, as cited in Section 1.2 above. Under the federal regulations, IRBs have the authority:

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

The IRB functions independently. Attempts to coerce or otherwise unduly influence the actions of the IRB are forbidden by policy, and are to be reported as described in Section 4.7. Likewise, the IRB must remain free from the influence of financial and other organizational interests. No individual with responsibility for the business and financial interests of the organization may serve on the IRB.

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

4.2 Roles and Responsibilities

4.2.1 Chair of the IRB

The University of Virginia Institutional Official (IO), in consultation with the [Director of the HRPP Office], appoints a Chair and Vice Chair(s) of the IRBs to serve for renewable [up to 5 year] terms. Any change in appointment, including reappointment or removal, requires written notification.

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

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

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

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

The IRB Chair advises the Institutional Official and the IRB Directors about IRB member performance and competence.

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

4.2.2 Vice Chair of the IRB

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

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

4.2.3 IRB Members

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

1. Completing member education and training, both initial and on-going (See Section 3.1).
2. Maintaining the confidentiality of IRB deliberations and research review by the IRB.
3. Conducting and documenting reviews of assigned research in a timely fashion.
4. Attending IRB meetings as scheduled.

Members should attend all meetings for which they are scheduled. If a member is unable to attend a scheduled meeting, they should inform an IRB Office staff member.

If an IRB member is to be absent for an extended period of time, he or she must notify the IRB at least 30 days in advance so that an appropriate alternate/replacement can be obtained. If the member has a designated alternate, the alternate can serve during the primary member's absence.

5. Recusing self from final deliberations and vote when s/he has a conflict of interest (Refer to section 21.2 for IRB Member conflict of interest policies).
6. Participating in subcommittees of the IRB if requested and available.
7. Conduct themselves in a professional and collegial manner.

The performance of IRB members will be reviewed every three years or sooner upon resignation from the IRB by the IRB Chair and the IRB Director. IRB members will receive formal documented feedback on the results of this review. Members who are not acting in accordance with the IRB's mission or not following policies and procedures or who have an undue number of absences may be removed.

4.2.4 Alternate members

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

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

Experienced alternate members may be designated by the Chair to conduct expedited reviews.

4.2.5 Subcommittees of the IRB

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

4.3 IRB Membership

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

The IRB will include members who are knowledgeable about and experienced working with vulnerable populations that typically participate in University of Virginia research.

The IRB must promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects; and possess the professional competence necessary to review specific research activities. The University of Virginia has procedures (See Section 7.4.1.1) that specifically outline the requirements of research plan review by individuals with appropriate scientific or scholarly expertise. A member of the IRB may fill multiple membership position requirements for the IRB.

Individuals from University of Virginia Office of Sponsored Programs, ResearchNET: (office of research development), Strategic Corporate Partners or the Licensing and Ventures Group may not serve as members of the IRB or carry out day-to-day operations of the review process. Individuals from these offices may provide information to the IRB and attend IRB meetings as invited guests.

4.4 Composition of the IRB

1. The IRB will have at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the organization.
2. The IRB will be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

3. In addition to possessing the professional competence necessary to review specific research activities, the IRB will be able to ascertain the acceptability of proposed research in terms of organizational commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB will therefore include persons knowledgeable in these areas.
4. If the IRB regularly reviews research that involves a vulnerable category of subjects (e.g., children, prisoners, pregnant women, or handicapped or mentally disabled persons), consideration will be given to the inclusion of one or more individuals on the IRB, who are knowledgeable about and experienced in working with these subjects.
5. Every nondiscriminatory effort will be made to ensure that the IRB does not consist entirely of men or entirely of women, including the organization's consideration of qualified persons of both sexes, so long as no selection is made to the IRB solely on the basis of gender. The IRB shall not consist entirely of members of one profession.
6. The IRB includes at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.
7. The IRB includes at least one member who is not otherwise affiliated with the organization and who is not part of the immediate family of a person who is affiliated with the organization.
8. The IRB includes at least one member who represents the general perspective of participants.
9. One member may satisfy more than one membership category.
10. The IRB Chair and Vice-Chairs are voting members of the IRB.
11. The Directors and staff of University of Virginia IRB Offices may be voting members of the IRB.

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

4.4.1 Appointment of Members to the IRB

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

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

Appointments are made for a one or three year terms depending on the position. Certain positions (e.g. study coordinator, medical student) are not renewable. Other appointments are

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

On an annual basis, the IRB Chair and the Director or their designee of the IRB Office reviews the membership and composition of the IRB to determine if they continue to meet regulatory and institutional requirements.

4.4.2 IRB Registration Updates

Changes in IRB membership will be reported to FDA and OHRP as follows:

1. A University of Virginia decision to disband a registered IRB that it is operating will be reported in writing within 30 days after permanent cessation of the IRB's review of DHHS-conducted or –supported research.
2. If an FDA-regulated IRB decides to review additional types of FDA-regulated products (e.g., to review device studies if it only reviewed drug studies previously) or to discontinue reviewing clinical investigations regulated by FDA, it must report this within 30 days of the change.
3. Within 90 days after changes regarding the contact person who provided the IRB registration information or the IRB Chair,
4. To register any additional IRB before it is designated under an FWA and reviews research conducted or supported by DHHS or regulated by FDA.

4.5 Use of Consultants

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

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

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

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

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

4.6 Liability Coverage for IRB Members

The University of Virginia, as an authorized agency of the Commonwealth of Virginia, participates in the Commonwealth's self-insured program which provides insurance coverage for employees and any other person authorized to act on behalf of University of Virginia for acts or omissions within the scope of their employment or authorized activity.

4.7 Reporting and Investigation of Allegations of Undue Influence

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

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

The IO ensures that a thorough investigation is conducted, and if the allegation is determined valid, that corrective action is taken to prevent additional occurrences. In the event that the allegation is regarding the IO, the matter is referred to the Provost for investigation and any necessary action.

5 Human Subject Research Determination

The responsibility for initial determination whether an activity constitutes human subject research rests with the investigator. The investigator should make this determination based on the definitions of “human subject” and “research” in Section 1.3. For guidance on whether an activity constitutes human subjects research, investigators should use the Determination of Human Subjects Research Form on the IRB-HSR website, or guidance on the IRB-SBS website . Because they will be held responsible if the determination is not correct, investigators may wish to submit the required documentation for confirmation that an activity does not constitute human subject research to the IRB office, if the determination is not clear. When research involves the use of coded private information or specimens, and the investigator makes an initial determination that the research does not include “human subjects”, the investigator must request confirmation in writing from the appropriate IRB office. All requests must include a sufficient description of the activity and the rationale for the investigator’s initial determination.

Determinations whether an activity constitutes human subject research will be made according to the definitions in Section 1.3 of this document. Determinations regarding activities that are either clearly human subject research or clearly not human subject research, may be made by an experienced IRB staff member. Determinations regarding less clear-cut activities will be referred to the IRB Chair, sub-committee or IO.

Documentation of all determinations made through the IRB Office will be recorded and maintained in the IRB Office. Email and other written requests will be responded to in writing and a copy of the submitted materials and determination letter/email will be kept on file.

6 Exempt Studies

All research using human subjects must be approved by the University of Virginia. However, certain categories of human subject research are exempt from IRB approval. Exempt research is subject to review for determination of exemption status. At the University of Virginia, exemptions are reviewed and granted by IRB Staff or Chair.

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

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

6.1 Limitations on Exemptions

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

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

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

6.2 Categories of Exempt Research

With the above-referenced limitations, research activities not regulated by the FDA (see Section 6.3 for FDA Exemptions) in which the only involvement of human subjects are determined to be in one or more of the following categories are exempt from IRB approval:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as
 - (i) research on regular and special education instructional strategies, or
 - (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
 - (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
 - (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation.
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (2), if:
 - (i) the human subjects are elected or appointed public officials or candidates for public office; or
 - (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

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

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

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

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

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

6.3 FDA Exemptions

The following categories of clinical investigations are exempt from the requirements for prior IRB review and approval:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article is subject to IRB review. [21 CFR 56.104(c)]

Note: See Section 13.2 for detailed discussion of this exemption.

2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR 56.104(d)]

6.4 Procedures for Exemption Determination

In order to obtain an exemption determination, investigators must submit:

1. The required form depending on IRB of record;
2. All recruitment materials (e.g., letter of invitation, recruitment script, flyer);
3. Consent form/disclosure/information sheet (when appropriate);
4. All surveys, questionnaires, instruments, etc. (when appropriate);
5. Letter(s) of permission from each non-University of Virginia site of performance; and
6. Verification of current human research protection training for all members of the research team, including the faculty advisor.

The IRB staff, member or Chair reviews all requests for exemptions and determines whether the request meets the criteria for exempt research.

To document the reviewer's determination of the request for exempt research, the reviewer completes the required form depending on IRB of record. The reviewer verifies whether the submission meets the definition of human subject research (See Section 5). If the request meets the definition of human subject research, the reviewer then determines whether or not the research is eligible for exemption. Although exempt research is not covered by the federal regulations, this research is not exempt from the ethical guidelines of the Belmont Report.

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

If there are interactions with participants, the reviewer should determine whether there should be a consent process that will disclose such information as:

- That the activity involves research.
- A description of the procedures.
- That participation is voluntary.
- Name and contact information for the researcher

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

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

Exempt determinations will include a termination date, with the maximum time allotted being 4 years. Investigators will be contacted every four years to determine if the study is to remain active. Investigators should report to any proposed modifications to the research during the course of the exempt study for a determination of whether or not the modified activity still qualifies for exemption. Finally, investigators must notify the IRB office when an exempt research project is complete so that the organization can maintain an accurate database of active research.

7 IRB Review Process

The IRB will review and ensure that University of Virginia research involving human subjects meets all required ethical and regulatory criteria for initial and continuing review and any modifications of approved research. The IRB may conduct their review using the following review methods:

- Expedited Review
- Review by Convened IRB (Full Board Review)

The following describe the procedures required for the review of research by the University of Virginia IRB. (See section 9 for a description of the procedures for review of research by non–University of Virginia IRBs.)

7.1 Definitions

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

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

1. The acceptability of the risk-to-benefit analysis or increases the level of risks to subjects
2. The research design or methods (adding procedures that are not eligible for expedited review (See Section 7.2.2) would be considered more than a minor change)
3. The number of subjects enrolled in the research (usually not greater than 10% of the total requested locally)
4. The qualifications of the research team
5. The facilities available to support safe conduct of the research
6. Any other factor which would warrant review of the proposed changes by the convened IRB

Quorum. A quorum of the IRB consists of a majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area. When research involving an investigational new drug is on the agenda for review, a physician should be included in the quorum.

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

approval of the suspended research study has expired, a continuing review is required before the study may resume.

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

7.2 Expedited Review

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

1. Some or all of the research appearing on the list of categories of research eligible for expedited review and found by the reviewer(s) to involve no more than minimal risk.
2. Minor changes in previously approved research during the period (of one year or less) for which approval is authorized. Note: review of minor changes does not alter the end-date of study approval.

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

7.2.1 Categories of Research Eligible for Expedited Review

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

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

The categories in this list apply regardless of the age of subjects, except as noted in category 2.

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

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

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

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

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or

decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

(b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week. (Note: Children are defined as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.)

(3) Prospective collection of biological specimens for research purposes by noninvasive means.

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

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

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an

invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

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

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

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

Categories 8 and 9 apply only to continuing review.

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

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

(b) Where no subjects have ever been enrolled at University of Virginia and no additional risks have been identified (Note: "no additional risks have been identified" means that neither the investigator nor the IRB has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB's most recent prior review.); **or**

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

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

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

7.2.2 Expedited Review Procedures

Under an expedited review procedure, the review may be carried out by the IRB Chair or by one or more reviewers designated by the Chair from among members of the IRB. IRB members who serve as designees to the IRB Chair for expedited review will be matched as closely as possible with their field of expertise to the study.

The Chair will designate a list of IRB members eligible to conduct expedited review. The designees must be experienced (having served on the IRB for at least one year) voting members or alternate members of the IRB. Selected reviewers will have the qualifications, experience and knowledge in types of research to be reviewed, as well as be knowledgeable of the requirements to approve research under expedited review. IRB members with a conflict of interest in the research (see Section 21.2) will not be selected.

When reviewing research under an expedited review procedure, the IRB Chair, or designated IRB member(s), will receive and review all documentation that would normally be submitted for a full-board review. This requirement applies to all categories of submissions including initial reviews, continuing reviews, and modifications. The reviewer determines and documents the regulatory criteria allowing use of the expedited review procedure in applicable review checklists and/or in the IRB’s electronic system. The reviewer(s) will complete the appropriate review checklist to determine whether the research meets the regulatory criteria for approval. The same criteria of approval apply to reviews conducted via expedited review as to those conducted by the convened board. If the research does not meet the criteria for expedited review, then the reviewer will indicate that the research requires full review by the IRB and the research study will be placed on the next available agenda for an IRB meeting.

In reviewing the research, the reviewers will follow the Review Procedures described in Sections 7.2 and 7.4 and may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure by the convened IRB (see Section 7.3).

If the reviewer determines the research may be approved, the reviewer documents that the research meets the regulatory criteria using the Review form/online system for approval and proceeds with the approval.

If modifications are required, the reviewer or responsible IRB staff member will notify the investigator via email /the IRB electronic system.

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

7.2.3 Informing the IRB

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

7.3 Convened IRB Meetings

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

7.3.1 IRB Meeting Schedule

The IRB meets on a regular basis throughout the year. The schedule for the IRB may vary due to holidays or lack of quorum. The schedule for IRB meetings is posted on the IRB websites. Special meetings may be called at any time by the Chair, IRB Director or the HRPP Directors.

7.3.2 Pre Review

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

7.3.3 Primary and Secondary Reviewers

After it has been determined that the submission is complete, an IRB Staff member with the assistance of the IRB Chair as needed, will assign submissions for review paying close attention

to the subject matter of the research, the potential reviewer's area/s of expertise and representation for any vulnerable populations involved in the research. Primary and secondary reviewers will be assigned to each submission and receive and review the full submission materials. Reviewers may be assigned several submissions or other items for review. When the IRB is presented with a research study which may be outside of the knowledge base or representative capacity of the IRB members, an outside consultant will be sought (See Section 4.5). Research studies for which appropriate expertise cannot be obtained for a given meeting will be deferred to another meeting when appropriate expertise is available.

Primary and secondary reviewers are responsible for:

1. Having a thorough knowledge of all of the details of the proposed research.
2. Performing an in-depth review of the proposed research.
3. Beginning the discussion of the proposed research at the convened meeting, by summarizing the proposed research, and leading the IRB through the regulatory criteria for approval. (See Section 7.4).
4. Making suggestions for changes to the proposed research, where applicable.
5. Completing all applicable IRB reviewer forms or certifications.

Secondary reviewers are paired with a primary reviewer for each submission. A secondary reviewer may be assigned to review the full submission materials or may be asked to review specified sections of the submission (e.g., the consent/assent/permission forms).

All IRB members receive and are expected to review all studies, not just those assigned as primary and secondary reviewers.

When it can be anticipated that the primary reviewer may be absent from the meeting, a new primary reviewer may be assigned, providing that they have sufficient time to review the materials in advance of the meeting. Additionally, an absent reviewer can submit their written comments for presentation at the convened meeting. A secondary reviewer may serve as primary reviewer in a given meeting. If an absent reviewer submits comments, those can indicate a recommendation regarding approval, but such recommendation will not be counted as a vote.

7.3.4 Materials received by the IRB

All required materials need to be submitted to the IRB office 9 business days prior to the convened meeting for inclusion on the IRB agenda. The meeting agenda will be prepared by the IRB Staff in consultation as needed with the IRB Director or IRB Chair. All IRB members receive the IRB agenda and research submission materials no later than 6 to 7 business days before the scheduled meeting to allow sufficient time for the review process.

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

- A research protocol

- The IRB Study Application (if applicable)
- Consent/parental or guardian permission/assent forms, letters or scripts (if applicable)
- Recruitment materials including advertisements intended to be seen or heard by potential subjects (if applicable)
- Supporting documents such as interview guides, surveys or other data collection tools (if applicable)
- Investigator brochure(s) (if applicable)

Additionally, for DHHS-supported multi-site clinical trials, the primary reviewer should receive and review a copy of the DHHS-approved sample informed consent document(s) (when one exists) and the complete DHHS-approved protocol/research plan (when one exists).

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

Reviewers will use an IRB reviewer checklist as a guide to completing their review.

7.3.5 Quorum

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

The IRB Chair, with the assistance of the IRB staff, will confirm that quorum is present before calling the meeting to order. The IRB Chair, with the assistance of the IRB staff, will be responsible to ensure that the IRB meeting remains appropriately convened. If a quorum is not maintained, either by losing a majority of the members, losing all non-scientific members or another required member, the IRB cannot take further actions or vote on regulatory determinations until quorum is restored, even if half of the members are still present.

The IRB Staff will document the arrival and departure for all IRB members and notify the IRB Chair if a quorum is not present. Attendance and vote count are documented or monitored by the IRB staff for each study. It is generally expected that at least one unaffiliated member and at least one member who represents the general perspective of participants (one individual can serve in both capacities) will be present at all IRB meetings. The IRB may, on occasion, meet without this representation; however, this should be the exception.

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

knowledgeable about and experienced with those subjects should be present during the review of the research.

When the IRB is presented with a research study which may be outside of the knowledge base or representative capacity of the IRB members, an outside consultant will be sought. Research studies for which appropriate expertise cannot be obtained for a given meeting will be deferred to another meeting when appropriate expertise is available.

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

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

7.3.6 Meeting Procedures

The IRB Chair will call the meeting to order, once it has been determined that a quorum is in place. The Chair will remind IRB members to recuse themselves from the discussion and votes by leaving the room when they have a conflict.

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

The IRB Staff take notes of the proceedings and are responsible for preparing the meeting minutes.

7.3.7 Guests

Investigators and research staff may be invited to the IRB meeting, at the discretion of the IRB, to make a brief presentation or to answer questions about proposed or ongoing research. The investigator/research staff may not be present for the deliberations or vote on the research.

(List regularly attending guests by title.)

The IRB Directors and staff regularly attend IRB meetings and may participate in the IRB discussion and deliberations, but may not vote unless they are serving as an IRB member for the meeting.

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

7.4 Criteria for IRB Approval of Research

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

- (1) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
- (3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disable persons, or economically or educationally disadvantaged persons.
- (4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by the Federal Regulations [45 CFR 46.116].
- (5) Informed consent will be appropriately documented, in accordance with, and to the extent required by the Federal Regulations [45 CFR 46.117].
- (6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- (7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- (8) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

7.4.1 Risk/Benefit Assessment

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

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

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

1. **Identify the risks** associated with the research, as distinguished from the risks of activities, diagnostic tests, treatments, or therapies the subjects would receive even if not participating in research;
2. **Determine whether the risks will be minimized** to the extent possible by evaluating the necessity of procedures that impart risk and whether the data could be gained by procedures that are already being performed for other purposes or by alternative procedures that impart less risk;
3. **Identify the anticipated benefits** to be derived from the research, both direct benefits to subjects and possible benefits to society, science and others;
4. **Determine whether the risks are reasonable in relation to the benefits**, if any, and assess the importance of the knowledge to be gained;

In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research - as distinguished from risks and benefits subjects would receive even if not participating in the research.

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

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

7.4.1.1 Scientific or Scholarly Review

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

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

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

Scientific or scholarly review can be delegated to a departmental or other appropriate review committee.

7.4.2 Equitable Selection of Subjects

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

- The purposes of the research;
- The setting in which the research occurs;
- Scientific and ethical justification for including vulnerable populations such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons;
- The scientific and ethical justification for excluding classes of persons who might benefit from the research; and
- The inclusion/exclusion criteria, and the procedures/materials intended for use for the identification and recruitment of potential subjects.

7.4.2.1 Recruitment of Subjects

The investigator will provide the IRB with a plan for recruitment of all potential subjects for approval. All recruiting materials will be submitted to the IRB, including advertisements, flyers, scripts, letters, information sheets and brochures. The IRB should ensure that the recruitment plan and materials appropriately protect the rights and welfare of the prospective subjects (e.g., do not present undue influence). See Section 7.5.10 for a discussion of IRB review of advertisements and Section 7.5.11 for a discussion of IRB review of payments.

7.4.3 Informed Consent

The IRB will ensure that informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.20. In addition, the IRB will ensure that informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27. The IRB will ensure, as part of its review, that the information in the consent document and process is consistent with the research plan, and, when applicable, the HIPAA authorization. See Section 11 below for detailed policies on informed consent.

7.4.4 Data and Safety Monitoring

For all research that is more than minimal risk, the investigator should submit a data and safety monitoring plan. The initial plan submitted to the IRB should describe the procedures for safety monitoring, reporting of unanticipated problems involving risks to subjects or others, descriptions of interim safety reviews and the procedures planned for transmitting the monitoring results to the IRB. This description should include information regarding an independent Data and Safety Monitoring Board (DSMB), if one exists, or an explanation why an independent data safety monitor is not necessary.

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

The factors the IRB will consider in determining whether the safety monitoring plan is adequate for the research are as follows:

1. Monitoring is commensurate with the nature, complexity, size and risk involved.
2. Monitoring is timely. Frequency should be commensurate with risk. Conclusions are reported to the IRB.
3. For low risk studies, continuous, close monitoring by the study investigator or an independent individual may be an adequate and appropriate format for monitoring, with prompt reporting of problems to the IRB, sponsor and regulatory bodies as appropriate.
4. Data and Safety Monitoring plans should specify:
 - The entity or person(s) who will perform the monitoring, and the independence or affiliation that the entity or person(s) has with the sponsor or investigator
 - The safety information that will be collected and monitored, including serious adverse events and unanticipated problems
 - The frequency or periodicity of review of safety data

- The procedures for analysis and interpretation of the data
 - The procedures for review of scientific literature and data from other sources that may inform the safety or conduct of the study
 - The conditions that trigger a suspension or termination of the research (i.e., stopping rules), if applicable
 - The procedures for reporting to the IRB, including a summary description of what information, or the types of information, that will be provided
5. For a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), the plan should describe:
- The composition of the board or committee. Generally, a DSMB should be composed of experts in all scientific disciplines needed to interpret the data and ensure subject safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease/condition and treatment under study should be part of the monitoring group or be available if warranted.
 - Frequency and content of meeting reports
 - The frequency and character of monitoring meetings (e.g., open or closed, public or private)
 - The Charter should be provided, when one exists

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

7.4.5 Privacy and Confidentiality

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

7.4.5.1 Definitions

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

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

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

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

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

7.4.5.2 Privacy

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

In developing strategies for the protection of subjects' privacy, consideration is given to:

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

7.4.5.3 Confidentiality

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

At the time of initial review, continuing review and with any requests for modification, the IRB assesses whether there are adequate provisions to protect data confidentiality. The IRB does this through the evaluation of the methods used to obtain, record, share, and store information about individuals who may be recruited to participate in studies and about subjects. The investigator will provide the IRB with a plan regarding the procedures to be taken to protect the confidentiality of research data and sensitive information. Additionally, the investigator will

provide information regarding information security procedures and plans to address the protection of paper documents, other physical media (e.g., audio or videotapes), and electronic data and information including the use, maintenance, storage, and transmission of information. The IRB will review all information received from the investigator and determine whether or not the confidentiality of research data is sufficiently protected. In some cases, the IRB may also require that a Certificate of Confidentiality be obtained to additionally protect research data (See Section 25.8) and/or obtain approval from the University of Virginia Information Security Office (InfoSec).

In reviewing confidentiality protections, the IRB shall consider whether or not the data or other information accessed or gathered for research purposes is sensitive and the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. The IRB in consultation with the InfoSec staff shall evaluate the effectiveness of proposed de-identification techniques, coding systems, encryption methods, methods of transmission, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections. In reviewing confidentiality protections, the IRB and the InfoSec staff shall also consider regulations and organizational requirements and policies regarding the use of information and information security.

Research regulated by the FDA that involves the use of electronic data collection/storage systems must comply with the requirements of 21 CFR Part 11.

7.4.6 Vulnerable Populations

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

For an extensive discussion about the IRB's review and approval process for individual populations of vulnerable subjects, please refer to Section 12.

7.5 Additional Considerations

7.5.1 Determination of Risk

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

risk levels; expedited reviewers will document the determination of risk level on the IRB reviewer form or certification checklist.

7.5.2 Period of Approval

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

IRB approval is considered to have lapsed at midnight on the expiration date of the approval (i.e., the expiration date is the last day research can be conducted). For a new study reviewed by the IRB, the approval commences on the date that the IRB conducts its final review of the study; that is, the date that the convened IRB or expedited reviewer approves the research or the date that it is verified that the requirements of the IRB have been satisfied following an action of "Conditions Required for Approval". The expiration date of the initial approval period, which is the date by which the first continuing review must occur, may be as late as one year after the last determination of approval or approvable with conditions..

For all continuing reviews of a research study subject to convened board review, the date the convened IRB or the date that the expedited reviewer conducts continuing review and approves the study (with or without conditions) determines the latest permissible date of the next continuing review.

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

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

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur by midnight of the date when IRB approval expires. If the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur.

7.5.3 Review More Often Than Annually

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

1. The probability and magnitude of anticipated risks to subjects.

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

In specifying an approval period of less than one year, the IRB may define the period with either a time interval or a maximum number of subjects either studied or enrolled. If a maximum number of subjects studied or enrolled is used to define the approval period, it is understood that the approval period in no case can exceed one year and that the number of subjects studied or enrolled determines the approval period only when that number of subjects is studied or enrolled in less than one year. If an approval period of less than one year is specified by the IRB, the reason for more frequent review must be documented in the minutes, the reviewer's checklist or electronic comments.

7.5.4 Independent Verification That No Material Changes Have Occurred

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

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

1. The probability and magnitude of anticipated risks to subjects.
2. The likely medical/psychological/social/legal/educational condition of the proposed subjects.
3. The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.
4. Concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources.

5. Investigators who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB.
6. Research without a routine monitoring plan.
7. Any other factors the IRB deems verification from outside sources is relevant.

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

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken (see Section 16 on Non-compliance).

7.5.5 Consent Monitoring

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

Such monitoring may be particularly warranted for:

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

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

If the IRB determines that consent monitoring is required, the IRB Members will determine the requirements for consent monitoring. The consent monitoring may be conducted by University of Virginia Post Approval Monitoring (PAM) Staff. The investigator and PAM Office will be notified of the IRB's determination and the reasons for the determination. PAM staff will make arrangements with the investigator for the monitoring of the consent process, typically for a specified number of subjects. When observing the consent process, the monitor will determine:

- Whether the informed consent process was appropriately conducted and documented;

- Whether the participant had sufficient time to consider study participation;
- Whether the consent process involved coercion or undue influence;
- Whether the information was accurate and conveyed in understandable language; and
- Whether the subject appeared to understand the information and gave their voluntary consent.

Following the monitoring, a report of the findings will be submitted to the IRB, which will determine the appropriate action to be taken.

7.5.6 Investigator Qualifications

The IRB research application asks specific questions regarding the investigator and research team's credentials to determine whether investigators and members of the research team are appropriately qualified to conduct the research. The IRB may rely upon other University of Virginia processes (e.g., credentialing) to inform this determination.

7.5.7 Investigator Conflicts of Interest (COI)

The IRB research application asks specific questions regarding the investigator and research team compliance with disclosure requirements and whether or not any COI management plans are in place. As part of its review process, the IRB will make a final determination as to whether any conflict of interest is adequately addressed and protects the human subjects in the research. The IRB has final authority to determine whether the declared COI and the management plan, if any, allow the study to be approved. (See Section 21 for a more detailed discussion of COI)

7.5.8 Institutional Conflicts of Interest

As with individual conflict of interest, the IRB has final authority to determine whether the Institutional Conflict, the Financial Interest, and the management plan, if any, allow the study to be approved. See Section 21.3 for a more detailed discussion of Institutional COI.

7.5.9 Significant New Findings

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

with the new information. The IRB may also require that former subjects be provided with the new information, e.g., if it impacts their rights or welfare.

7.5.10 Advertisements and Recruitment Materials

The IRB must review and approve any and all advertisements prior to posting and/or distribution for studies that are conducted under the purview of the University of Virginia. The IRB will review:

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

This information should be submitted to the IRB with the initial application or, if recruitment is proposed after study approval, as a modification request.

The IRB reviews the material to assure that the material is accurate and is not coercive or unduly optimistic, creating undue influence to the subject to participate. This includes but is not limited to:

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

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

1. The name and address of the investigator and/or research facility.
2. The condition being studied and/or the purpose of the research.

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

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

Directory listings of research such as ClinicalTrials.gov are not considered advertisements and therefore do not require IRB review and approval if the listing is limited to the following basic trial information: title, purpose of the study, research plan summary, basic eligibility criteria, study site location(s), and how to contact the study site for further information.

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

7.5.11 Payments to Research Subjects

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

Investigators who wish to pay research subjects must submit to the IRB the amount and schedule of all payments. Investigators should indicate in their research project application the justification for such payment. Such justification should substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject and do not constitute (or appear to constitute) undue pressure on the potential subject to volunteer for the research study.

The IRB must review both the amount of payment and the proposed method and timing of disbursement to assure that neither entails problems of coercion or undue influence.

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

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

Unless the study is confidential, the University of Virginia Procurement Office requires identifying information to issue checks, cash, or gift certificates to subjects. The consent form must inform subjects that they will be asked to provide their Social Security Number to receive payment.

7.5.12 Non-Monetary Gifts and Incentives

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

If subjects will be provided with non-monetary gifts or tokens of appreciation, such as totes, books, toys, or other such materials, the item and approximate retail value must be submitted to the IRB.

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

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

7.5.13 State and Local Laws

The IRB considers and adheres to all applicable state and local laws in the jurisdictions where the research is taking place. The IRB relies on the University of Virginia Counsel for the interpretation and application of Virginia law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research. The IRB will ensure that consent forms are consistent with applicable state and local laws.

7.6 Possible IRB Actions

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

Approvable with Conditions The research, proposed modification to the previously approved research, or other item is approved but conditions must be satisfied before the approval becomes effective.

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

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

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

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

When the convened IRB approves research with conditions, the IRB may designate the IRB Chair (and/or other qualified individual(s)) to review responsive materials from the investigator and determine that the conditions have been satisfied. If the conditions have not been satisfied, or are only partially satisfied, the responsive materials must be referred to the convened IRB for review. When an expedited reviewer approves research with conditions, the original expedited reviewer (and/or other qualified individual(s)) will receive the response materials.

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

- The date when the IRB determined that the criteria for approval were satisfied (i.e., the "approval date");
- The date when verification was made that all IRB conditions have been satisfied (i.e., the "effective date"), and;
- For initial approval and continuing reviews, the date by which continuing review must occur.

The date of approval is the date the conditions were determined to be met. If the research expires before the conditions are reviewed and approved, all research activities must stop until approval is obtained.

The IRB will be informed of the outcome of the review of the investigator's response in the agenda of a future meeting.

Deferred. (*This action is sometimes referred to as tabled.*) This action is taken by the IRB when modifications are required (of the nature or amount that the full IRB cannot make or specify

exact changes or parameters), or additional information or clarification is needed in order to determine that one or more criteria for approval are satisfied (e.g., the risks and benefits cannot be assessed with the information provided).

The deferral and the basis for the deferral is documented in the IRB minutes (for convened review) or Reviewer Checklist (for expedited review) and is communicated to the investigator in writing.

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

Disapproved. The IRB may determine that the proposed research cannot be conducted at University of Virginia or by employees or agents of University of Virginia or otherwise under the auspices of University of Virginia. Disapproval can only be decided at the convened IRB meeting. An expedited reviewer cannot disapprove a study.

Approval in Principle. As per federal regulations, [45CFR46.118], there are circumstances in which a sponsoring agency may require certification of IRB approval as a condition of submitting for or releasing funds but before definitive plans for the involvement of human subjects have been developed (e.g., certain training grants or grants in which the procedures involving human subjects are dependent on the completion of animal studies or instrument development). In these circumstances, the IRB may grant “approval in principle” without having reviewed the as yet undeveloped procedures or materials. The IRB Chair or designee will review the available information (i.e., the grant or proposal and any supplemental information provided by the investigator) and, if appropriate, will provide certification of IRB approval in principle. If the proposal is funded, the investigator must submit such materials for approval at least [60] days before recruiting human subjects into the study, or into any pilot studies or pre-tests.

7.7 Continuing Review

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

7.7.1 Continuing Review Process

As a courtesy to investigators, the IRB staff will send out renewal notices to investigators approximately two months and again one month in advance of the expiration date; however, it is the investigator’s responsibility to ensure that the continuing review of ongoing research is

approved prior to the expiration date. By federal regulation, no extension to that date can be granted.

Investigators must submit the following for continuing review:

- The current protocol and IRB application
- The current consent document
- The most recent report(s) from the DSMB or DMC (if applicable);
- The most recent multi-site progress report (if applicable);
- Copy of any audits performed during the review period and
- The continuing review status report.

IRB members can request the study file or any additional materials from the IRB staff prior to the meeting or during the expedited review process.

7.7.2 Approval Considerations

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

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

7.7.3 Convened Board Review

In conducting continuing review of research not eligible for expedited review, all IRB members are provided with access to all of the materials listed in Section 7.7.2 and are responsible for reviewing the protocol, the current consent documents or materials, the status report, and, if applicable, the data and safety monitoring report, multi-site study progress reports. The primary and secondary reviewers are responsible for reviewing the complete materials submitted for continuing review and is given access to the complete IRB file and relevant IRB meeting minutes. At the meeting, the Primary and Secondary Reviewers assist the Chair in leading the IRB through the completion of the regulatory criteria for approval in the IRB reviewer or certification checklist.

Review of currently approved or newly proposed consent documents must occur during the scheduled continuing review of research by the IRB, but consent documents should be

reviewed whenever new information becomes available that may require modification of information in the consent document.

7.7.4 Expedited Review

In conducting continuing review under expedited procedures, the reviewers receive all of the previously noted materials. The reviewer(s) complete the IRB reviewer or certification checklist to determine whether the research meets the criteria allowing continuing review using the expedited procedure, and if so, whether the research continues to meet the regulatory criteria for approval.

Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9) (see Expedited Review Categories in Section 7.2.1). It is also possible that research activities that previously qualified for expedited review, have changed or will change, such that expedited IRB review would no longer be permitted for continuing review.

7.7.5 Possible IRB Actions after Continuing Review

As with Initial Review, at the time of Continuing Review, the Convened IRB or IRB Member(s) conducting expedited review may take any of the following actions (see Section 7.6 for a detailed description of these actions):

1. Approved
2. Approvable with Conditions
3. Deferred

Additionally, the convened IRB may vote to disapprove the study. If an IRB member conducting expedited review believes that the study should be disapproved, it will be referred to the convened board for review. If the IRB has significant concerns, the IRB may vote to suspend or terminate the research (See Section 8 for a detailed discussion of suspensions and terminations).

If a research study receives Approvable with Conditions at the time of the Continuing Review, the IRB will specify whether any conditions need to be satisfied before an investigator can continue particular research activities related to those conditions or requirements that must be adhered to until the conditions of approval have been satisfied. For example, if at the time of continuing review, the IRB requires the investigator to change the research protocol to include a specific new procedure for screening prospective subjects, the IRB could approve the research with the following condition: research activities involving currently enrolled subjects may continue, but no new subjects may be enrolled until a designated IRB member reviews a revised protocol and verifies that the protocol includes the new screening procedure. Additionally, the IRB may specify a time period, such as 1, 2, or 3 months, for the condition/s to

be satisfied as long as the activity with conditions is not begun/restarted until approval is granted.

7.7.6 Lapses in Continuing Review

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

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

When the IRB approves research with conditions at the time of continuing review before the expiration date of the preceding IRB approval period, IRB approval does not lapse if the investigator needs additional time – beyond the date on which the preceding IRB approval would have expired – to satisfy some or all of the IRB’s conditions. However, the investigator and the IRB should make every effort to resolve any conditions and finalize approval in as timely a manner as possible.

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

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

restrictions. If the IRB decides that already enrolled subjects should continue to receive the interventions that were being administered to subjects under the research project, data collection (especially safety information) should also continue for such subjects.

When there is insufficient time to obtain an IRB determination (e.g., the study regimen includes daily administration of an investigational agent), the investigator may make an initial determination, in consultation with the subjects' treating physician, if appropriate. In such cases, the investigator must, as soon as possible, contact the IRB office and submit a request for confirmation that the IRB agrees with the determination. The IRB Chair or designee will review the request and provide a determination. In the event that the IRB does not agree with the investigator's determination, or only agrees in part (e.g., agrees that some but not all of the activities are in the best interests of subjects), the IRB will notify the investigator who must then comply with the IRB's requirements or request a re-review of the determination by providing additional justification or information that the IRB may not have considered.

7.8 Modification of an Approved Protocol

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

Modifications may be permanent (Protocol Modification) which make changes to the protocol for all remaining subjects or temporary (Protocol Exceptions) circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient(s)/subject(s) (examples: patient/subject is allergic to one of the medications provided as supportive care; patient/subject is not eligible in a direct benefit study). Usually an Exception is a change that is planned and has prior agreement from the sponsor. See Section 7.8.5 for details on Protocol Exceptions.

(Note: Protocol Deviations [see Section 14.1] are unplanned and are reported to the IRB after the fact.)

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

7.8.1 Procedures

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

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

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

7.8.2 Convened Board Review of Modifications

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

All IRB members are provided and review all documents provided by the investigator.

At the meeting, the Primary Reviewer presents an overview of the proposed modifications and assists the IRB Chair in leading the IRB through the completion of the regulatory criteria for approval. The IRB will also determine whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

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

7.8.3 Expedited review of Modifications

An IRB may use expedited review procedures to review minor changes in ongoing previously-approved research during the period for which approval is authorized. An expedited review may be carried out by the IRB Chair and/or experienced designee(s) among the IRB members.

The reviewer(s) complete the appropriate IRB reviewer or certification checklist to determine whether the modifications meet the criteria allowing review using the expedited procedure, and if so, whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

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

7.8.4 Possible IRB Actions after Modification Review

As with Initial Review, at the time of Continuing Review, the Convened IRB or IRB Member(s) conducting expedited review may take any of the following actions (see Section 7.6 for a detailed description of these actions):

1. Approved
2. Approvable with Conditions
3. Deferred

Additionally, the convened IRB may vote to disapprove the proposed changes. If an IRB member conducting expedited review believes that the proposed modifications should be disapproved, they will refer the proposed modification to the convened board for review. If the proposed changes raise significant concerns on the part of the IRB, the IRB may vote to suspend or terminate the research (See Section 8 for a detailed discussion of suspensions and terminations).

7.8.5 Protocol/Research Plan Exceptions

Protocol/Research Plan exceptions are circumstances in which the investigator wishes to deviate from eligibility criteria or one or more of the specific procedures called for in a research plan. Unlike modifications that apply to all subsequent subjects in the research, a protocol/research plan exception only applies to a specific subject or group of subjects.

Exceptions are planned, and the investigator gets approval from the sponsor and the IRB ahead of time. For sponsored research, prior approval from the sponsor is generally required. Depending on the nature of the exception, an expedited review is possible. In order to be approved under expedited review exceptions must not increase risk or decrease benefit, change the risk/benefit analysis, negatively affect the participant's rights, safety, welfare, or negatively affect the integrity of the resultant data. Review of exceptions that represent more than minor changes or risks levels greater than minimal must be done at a convened meeting of the IRB.

Procedures for exceptions are the same as for a Protocol Modification. The investigator must submit a modification request along with any revised documentation to be presented to the subject(s) and documentation of sponsor approval, if applicable.

The only time a protocol/Research Plan exception would not require prior sponsor or IRB approval is when the exception is necessary to avoid an immediate hazard to the participant. In such cases, the exception must be submitted to the IRB as soon as possible.

7.9 Closing a Research Study

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

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

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

Investigators may submit study closures to the IRB using a closure form . With closure submissions, the investigator must provide a summary of the research activity and any findings available at that time.

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

The IRB will provide a Receipt Acknowledgment of any Closure documentation received from the study team and note the closure in the IRB files. Reporting IRB Actions

All IRB actions are communicated to the investigator, and/or designated contact person for the research study, in writing within ten (10) working days via a Approval/Assurance form prepared by the IRB staff and signed by the IRB Chair or designated IRB member. For an approval, along with written notification of approval, a copy of the approved consent/assent/permission form/s (if applicable) will be shared with the study team. For approval with conditions, the notification will include a listing of the conditions that must be satisfied. For a deferral, the notification will include the modifications and/or clarifications required along with the basis for requiring those modifications. For a disapproval, termination or suspension, the notification will

include the basis for making that decision and give the investigator an opportunity to respond in person or in writing.

All letters to investigators must be available in the study files maintained by the IRB.

The IRB reports its findings and actions to the organization in the form of its minutes, which are distributed by IRB staff to the University of Virginia Institutional Official.

7.10 Failure to Respond

Failure to submit a response to IRB requirements for an unapproved protocol within 6 months of the IRB date of determination may result in administrative withdrawal of the IRB file (for new study submissions). When research has IRB approval, and an investigator fails to respond to requirements related to a subsequent submission (e.g., a request for modification), the IRB Chair or IRB Staff member will review the circumstances, including any potential impact on human subjects, and will contact the investigator to try to secure a response. If the investigator continues to be unresponsive, the failure of the investigator may be considered non-compliance and will be reviewed in accordance with the procedures in Section 16. The investigator will receive notification, including an explanation. An extension beyond 6 months may be granted by the IRB if sufficient cause is provided by the investigator.

7.11 Appeal of IRB Decisions

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

In cases where there is disagreement between the IRB and the investigator regarding the nature and extent of the requested changes or the necessity of or basis for a suspension or termination, and these disagreements cannot be resolved, the investigator and/or the IRB may make an appeal to the IO for a resolution of the matter. The IO may organize a meeting to help facilitate discussion between the IRB and the investigator. While the IO may provide input and make recommendations to the investigator and IRB for expeditious resolution of the matter, final determinations for approval/disapproval remain under the purview of the IRB.

Because the IO is responsible for policies and procedures followed by the IRB, the IO may review IRB decisions to ensure that the decision-making process is appropriate. If the IO has concerns regarding the process that the IRB has followed in making a decision, he/she may request that the IRB reconsider the decision. However, the IO cannot overrule an IRB decision.

7.12 Research Previously Approved By Another IRB

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

Research approved as exempt at the previous institution will be reviewed according to the procedures in Section 6. All other research must be submitted as if it were undergoing initial review and will be reviewed under expedited review or by the convened IRB. Research that solely involves the analysis of existing identifiable data may be considered under Expedited Review Category 5.

For research transfers where stopping research interventions might harm subjects, the investigator can request permission from the IRB to continue research interventions under the oversight of the prior organization's IRB until final University of Virginia approval is obtained.

8 Study Suspension, Termination and Investigator Hold

8.1 Suspension/Termination

IRB approval may be suspended or terminated if research is not being conducted in accordance with IRB or regulatory requirements or has been associated with unexpected problems or serious harm to subjects. (See Section 15 for a discussion of unanticipated problems and Section 16 for a discussion of non-compliance.)

Suspension of IRB approval is a directive of the convened IRB, IRB Chair or IO/IO designee to temporarily stop some or all previously approved research activities. Suspensions made by the IRB Chair or IO/IO designee must be reported to a meeting of the convened IRB. Suspended research studies remain open and require continuing review. Investigators must continue to provide reports on adverse events and unanticipated problems to both the IRB and sponsors just as if there had never been a suspension (i.e., all events that need to be reported during a study need to continue to be reported during the suspension period).

When approval of some or all research activities is suspended by the IRB, the IRB will consider notification of subjects and any actions necessary to ensure that the rights, safety, and welfare of subjects are appropriately protected.

The IRB shall notify the investigator in writing of suspensions and shall include a statement of the reasons for the IRB's actions and any requirements or conditions associated with the suspension (e.g., notification of subjects). The investigator shall be provided with an opportunity to respond in person or in writing.

Suspensions of IRB approval must be reported promptly to the IO, sponsors including federal department or agency heads, and federal oversight agencies according to applicable federal and organizational requirements. See Section 14 for a detailed discussion of reporting requirements.

Termination of IRB approval is a directive of the convened IRB to permanently stop all activities in a previously approved research study. Terminated research studies are closed and no longer require continuing review. Terminations of IRB approval of research studies must be made by the convened IRB.

When study approval is terminated by the IRB, in addition to stopping all research activities, the IRB will consider notification of subjects and any actions necessary to ensure that the rights, safety, and welfare of subjects are appropriately protected.

The IRB shall notify the investigator in writing of a study termination and shall include a statement of the reasons for the IRB's actions and any requirements associated with the termination (e.g., notification of subjects). The investigator shall be provided with an opportunity to respond in person or in writing.

Terminations of IRB approval must be reported promptly to the IO, sponsors including federal department or agency heads, and federal oversight agencies according to applicable federal

and organizational requirements. See Section 14 for a detailed discussion of reporting requirements.

Note: Suspension or termination of research studies approved by the IRB can also be issued by Organization officials acting outside of and unrelated to the interests of the IRB (i.e., not necessarily related to protecting the rights and welfare of study participants). Such Organization actions can be made by, for example, the IO, the Provost, Department Chairs or School Deans. The investigator must report any suspension or termination of the conduct of research to the IRB. The IRB determines if suspension or termination of IRB approval is warranted and notifies the Investigator.

8.2 Investigator Hold

An investigator may request an investigator hold when the investigator wishes to temporarily or permanently stop some or all approved research activities. Such a hold is initiated by an investigator, but must be immediately reported to the IRB so that the IRB can consider whether any additional actions are necessary to protect subjects. Investigator holds are not equivalent to IRB suspensions or terminations.

8.2.1 Procedures

1. Investigators must notify the IRB in writing that:
 - a. They are voluntarily placing a study on hold
 - b. A description of the research activities that will be stopped
 - c. Proposed actions to be taken to protect current participants
 - d. Actions that will be taken prior to IRB approval of proposed changes in order to eliminate apparent immediate risk of harm
2. Upon receipt of written notification from the investigator the IRB Director or designee places the research on the next available agenda for review.
3. The IRB Chair and/or Director or designee, in consultation with the investigator, determines whether any additional procedures need to be followed to protect the rights and welfare of current participants as described in “Protection of currently enrolled participants”(see Section 8.3).
4. The IRB Chair and/or Director or designee, in consultation with the investigators, determine how and when currently enrolled participants will be notified of the hold.
5. Investigators may request a modification of the research on hold by submitting a request for a modification to previously approved research.

8.3 Protection of Currently Enrolled Participants

Before a study hold, termination, or suspension, is put into effect the IRB Chair, Director, or IRB considers whether any additional procedures need to be followed to protect the rights and welfare of current participants. Such procedures might include:

- Transferring participants to another investigator/site
- Making arrangements for clinical care outside the research
- Allowing continuation of some research activities under the supervision of an independent monitor
- Requiring or permitting follow-up of participants for safety reasons
- Requiring adverse events or outcomes to be reported to the IRB and the sponsor
- Notification of current participants
- Notification of former participants

9 Research overseen by a non- UVA IRB of Record

9.1 UVA Investigator Responsibilities

Prior to submitting the application to the non-UVA IRB, the UVA investigator must satisfy University of Virginia requirements for the research. Even though the UVA IRB will not serve as the IRB of Record, they are responsible for verifying that other compliance and educational requirements are met.

9.2 UVA IRB Responsibilities

When the submission packet is received, the IRB Director or designee reviews the application materials. The following is reviewed:

- Eligibility to use external IRB review
- Review of investigator and study staff (confirmation of training, COI etc.)
- Review of non- IRB Compliance reviews/ approvals (e.g. Radiation safety, pharmacy, etc.)
- UVA Departmental Chair certification of scientific merit
- HIPAA compliance if the IRB-HSR will serve as the HIPAA Privacy Board

Once the above are reviewed by the IRB Director or designee and determined to be acceptable, the investigator will be notified that they may move forward with their submission to the non-UVA IRB. This approval will also be shared with other UVA offices via CR Connect, IRB Online, IRB Pro and iProtocol. The UVA IRB will provide the UVA PI with training certification for all UVA study personnel if requested. If not included with the IRB Reliance Agreement the UVA study team will also be provided with the UVA local language to be included in the IRB approved consent from the IRB of Record.

9.3 Responsibilities after the study is open to enrollment at UVA

After the research has begun any reports of UVA site monitoring activities which have any findings that potentially impact human subject protections must be shared with the UVA IRB.

Changes in study personnel must be submitted to University of Virginia IRB with the continuation status report or IRB Update Report. No personnel may begin study responsibilities prior to completing human subject research protection training.

UVA retains responsibility for Post Approval Monitoring. The study team will be required to submit PAM reports to the IRB of Record per their policies and procedures.

Additional responsibilities:

10 Documentation and Records

University of Virginia prepares and maintains adequate documentation of the IRB's activities. All records are accessible for inspection and copying by authorized representatives of the FDA, OHRP, sponsors, and other authorized entities at reasonable times and in a reasonable manner.

10.1 IRB Records

IRB records include, but are not limited to:

1. Written operating procedures
2. IRB membership rosters
3. Training records documenting that investigators, IRB members, and IRB staff have fulfilled University of Virginia's human subject training requirements
4. IRB correspondence including reports to regulatory agencies
5. IRB Study Records (Study Files) including correspondence with investigator and research team
6. Documentation of exemptions including exemptions related to emergency uses.
7. Convened IRB meeting minutes
8. Documentation of review by another institution's IRB when appropriate.
9. Documentation of cooperative review agreements, e.g., Memoranda of Understanding (MOUs).
10. Federal Wide Assurances.
11. IRB Registrations.
12. Documentation of complaints and any related findings and/or resolution.

10.2 IRB Study Files

The IRB maintains a separate IRB study file for each research application (study) that it receives for review. Research studies are assigned a unique identification number by the IRB Staff and entered into the IRB tracking system.

Accurate records are maintained of all communications to and from the IRB. Copies are filed in the study file. University of Virginia IRB maintains a separate file for each research study that includes, but is not limited to:

1. Research plan and all other documents submitted as part of a new study application.
2. Research plan and all other documents submitted as part of a request for continuing review or closure of research application.
3. Documents submitted and reviewed after the study has been approved, including modification requests, protocol/research plan exception requests, proposed

advertisements, data and safety monitoring reports, and reports of protocol/research plan violations, complaints, non-compliance, unanticipated adverse device events and unanticipated problems.

4. Copy of IRB-approved Consent/Assent/Permission Forms
5. DHHS-approved sample consent form document and research plan, when they exist
6. IRB reviewer forms (when expedited review procedures are used)
7. Documentation of scientific or scholarly review (if available).
8. Documentation of type of IRB review. For exempt determinations and expedited review, this will include the category under which the review is allowed.
9. For expedited review, documentation of any findings and determinations required by the regulations and study-specific findings supporting those determinations, including, but not limited to, waiver or alteration of consent, waiver of documentation of consent, research involving pregnant women, fetuses, and neonates, research involving prisoners, and research involving children. For research reviewed by the convened board these findings and determinations are recorded in the minutes.
10. For expedited review, documentation of the risk determination and period of approval. For research reviewed by the convened board these determinations are recorded in the minutes.
11. Documentation of all IRB review actions.
12. Notification of expiration of IRB approval to the investigator and requirements related to the expiration.
13. Notification of suspension or termination of research.
14. Copies of approval letters and forms that describe any requirements that the investigator must satisfy before beginning the study.
15. IRB correspondence to and from research investigators.
16. All other IRB correspondence related to the research.
17. For devices, documentation of determination by IRB of significant risk/non-significant risk.
18. Reports of unanticipated problems involving risk to subjects or others.
19. Documentation of audits, investigations, reports of external site visits.

10.3 The IRB Minutes

Proceedings are written and available for review by the next regularly scheduled IRB meeting. After the review period for minutes has lapsed, the minutes must not be altered by anyone including a higher organizational authority.

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

Minutes of IRB meetings must contain sufficient detail to show:

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

Note: The attendance list shall include those members present at the beginning of the meeting. The minutes will indicate, by name, those members who enter or leave the meeting. The vote on each action will reflect the numbers of members present for the vote on that item. Members who recuse themselves because of conflict of interest are listed by name and the reason documented.

2. The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area.
3. Business Items discussed and any education provided.
4. Continuing Education
5. Actions taken, including separate deliberations, actions, and votes for each research study undergoing review by the convened IRB.
6. Vote counts on these actions (Total Number Voting; Number voting for; Number voting against; Number abstaining; Number of those recused)
7. Basis or justification for actions disapproving or requiring changes in research
8. Summary of controverted issues and their resolution
9. Approval period for initial and continuing reviews, including identification of research that warrants review more often than annually and the basis for that determination
10. Risk determination for initial and continuing reviews, and modifications when the modification alters the prior risk determination
11. Justification for deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document.
12. Study-specific findings supporting that the research meets each of the required criteria when approving a consent procedure that does not include or that alters some or all of

the required elements of informed consent, or when waiving the requirement to obtain informed consent altogether

13. Study-specific findings supporting that the research meets each of the required criteria when the requirements for documentation of consent are waived
14. Study-specific findings supporting that the research meets each of the criteria for approval for vulnerable populations under any applicable Subparts.
15. Significant risk/non-significant risk device determinations and the basis for those determinations.
16. Determinations of conflict of interest and acceptance or modification of conflict management plans.
17. Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research.
18. Review of interim reports, e.g., unanticipated problems or safety reports; modification requests; report of violation/deviations; serious or continuing non-compliance; suspensions/terminations, etc.
19. A list of research approved under expedited review procedures since the time of the last such report.
20. An indication that, when an IRB member or alternate has a conflicting interest (see Section 21.2) with the research under review, the IRB member or alternate was not present during the final deliberations or voting.
21. Key information provided by consultants will be documented in the minutes or in a report provided by the consultant.

10.4 IRB Membership Roster

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

1. Name.
2. Earned degrees.
3. Employment or other relationship between each member and the organization (i.e., affiliated or non-affiliated). To be categorized as non-affiliated, neither the member nor an immediate family member of the member may be affiliated with the University of Virginia.
4. Status as scientist or non-scientist. Members whose training, background, and occupation would incline them to view scientific activities from the standpoint of someone within a behavioral or biomedical research discipline are considered a scientist for the purposes of the roster, while members whose training, background, and

occupation would incline them to view research activities from a standpoint outside of any biomedical or behavioral scientific discipline are considered a nonscientist.

5. Indications of experience, such as board certifications, licenses, and areas of practice sufficient to describe each member's chief anticipated contributions to IRB deliberations.
6. Representative capacities of each IRB member; including which IRB member(s) is a prisoner representative, and which IRB members are knowledgeable about or experienced in working with children, pregnant women, cognitively impaired individuals, and other vulnerable populations commonly involved in University of Virginia research.
7. Role on the IRB (Chair, Vice-Chair, etc.)
8. Voting status
9. For alternate members, the primary member or class of members for whom the member could substitute

The IRB office must keep the IRB membership list current. The IRB Director or designee will report changes in IRB membership to OHRP/FDA within 90 days of the change.

10.5 Documentation of Exemptions

Documentation of verified exemptions consists of the reviewer's citation of a specific exemption category as detailed in Section 6.

10.6 Documentation of Expedited Reviews

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

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

10.7 Access to IRB Records

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

1. All IRB records are kept secure in locked filing cabinets or locked storage rooms. Doors to the IRB Offices are closed and locked when the rooms are unattended.

2. Ordinarily, access to all IRB records is limited to the HRPP Director, IRB Chairs/Vice Chairs, IRB members, IRB Directors, IRB staff, PAM and Education Staff, authorized organizational officials, and officials of federal and state regulatory agencies (e.g., OHRP and FDA). Research investigators are provided reasonable access to files related to their research. Appropriate accreditation bodies are provided access. All other access to IRB records is limited to those who have legitimate need for them, as determined by the IO and IRB Director.
3. Records are accessible for inspection and copying by authorized representatives of federal regulatory agencies during regular business hours.
4. Records may not be removed from the IRB Office; however, the IRB staff will provide copies of records for authorized personnel if requested.
5. All other access to IRB study files is prohibited.

10.8 Record Retention

In order to comply with the requirements of OHRP, FDA, and HIPAA, IRB records are maintained at the facility for at least three (3) years after completion of the research. If the study is regulated by HIPAA and a Waiver of HIPAA authorization was granted the file will be kept for six (6) years after completion of the research.

IRB records for approved research cancelled without participant enrollment will be retained at the facility for at least 3 years after closure.

After that time those records will be shredded or otherwise destroyed.

11 Obtaining Informed Consent from Research Subjects

No investigator conducting research under the auspices of the University of Virginia may involve a human being as a subject in research without obtaining the legally effective informed consent of the subject or the subject's legally authorized representative unless a waiver of consent has been approved by the IRB in accordance with Section 11.9 of these procedures. Except as provided in Sections 11.10 and 11.11 of these procedures, informed consent must be documented by the use of a written consent form approved by the IRB. The written consent may be obtained electronically. If the study is regulated by the FDA the eConsent platform must be Part11 compliant.

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

The following procedures describe the requirements for obtaining consent from participants in research conducted under the auspices of the University of Virginia.

11.1 Definitions

Legally Authorized Representative. A legally authorized representative (LAR) is an individual or body authorized under applicable law to provide permission on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

Research conducted in Virginia:

The definition of an LAR for adults (see "Guardian" sec 12.1 for LARs for minors) are set out in the Virginia Health Care Decisions Act, Va. Code 54.1-2981 *et seq.*

The term "Agent" below is defined in Va. Code 54.1-2982; the remaining LARs are listed in Va. Code 54.1-2986.

If an adult has been determined to be incapable of making an informed decision (*see below for determination of incapacity requirements*), the list below indicates who may serve as an LAR, in decreasing order of priority:

1. the *agent* appointed under an advance directive, as defined in § [54.1-2982](#), executed by the prospective subject, provided the advance directive authorizes the agent to make decisions regarding the prospective subject's participation in human research;
"Agent" means an adult appointed by the declarant under an advance directive, executed or made in accordance with the provisions of § 54.1-2983, to make health care decisions for him, including visitation, provided the advance directive makes express provisions for visitation and subject to physician orders and policies of the institution to which the declarant is admitted. The declarant may also appoint an adult to make, after the declarant's death, an anatomical gift of all or any part of his body pursuant to Article 2 (§ 32.1-289 et seq.) of Chapter 8 of Title 32.1.

2. a legal guardian;
3. a spouse, except where a suit for divorce has been filed and the divorce decree is not yet final;
4. an adult child;
5. a parent;
6. an adult brother or sister; or
7. any other relative in the descending order of blood relationship.

Determinations of incapacity: See Va. Code 54.1-2983.2. For patients of UVA Health System, see Medical Center Policy No. 0024:

An adult is “incapable of making an informed decision” when he is unable to understand the nature, extent and probable consequences of a proposed decision or is unable to make a rational evaluation of the risks and benefits of a proposed decision as compared with the risks and benefits of alternatives to that decision, or is unable to communicate such understanding in any way. If two physicians or one physician and one clinical psychologist have, upon personal examination determined that a patient is incapable of making an informed decision for a specific course of treatment, the procedures set out in Figure 2 of the Medical Center Policy No. 0024 shall be followed. The second physician or psychologist shall not be otherwise involved in the treatment of the patient, unless such an independent physician or psychologist is not reasonably available.

The second capacity assessment is **not** required if the patient is unconscious or experiencing a profound impairment of consciousness due to trauma, stroke, or other acute physiological condition.

Research conducted outside Virginia: The IRB will consult with the Office of University Counsel to determine who under applicable law is authorized to consent on behalf of another person to undergo procedures in this research study or class of studies.

11.2 Basic Requirements

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

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

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

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

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

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

11.3 Informed Consent Process

Informed consent must be obtained under the following circumstances:

1. Informed consent may only be obtained from subjects who have the legal and mental capacity to give consent. For subjects without that capacity, permission must be obtained from a legal guardian or a legally authorized representative.
2. The informed consent process provides the prospective subject (or legally authorized representative) with sufficient opportunity to read the consent document, when applicable.
3. The informed consent process shall be sought under circumstances that provide the subject (or legally authorized representative) with sufficient opportunity to consider whether or not to participate.
4. The informed consent process shall be sought under circumstances that minimize the possibility of coercion or undue influence.

5. The informed consent information must be presented in language that is understandable to the subject (or legally authorized representative). To the extent possible, the language should be understandable by a person who is educated to 8th grade level and layman's terms shall be used in the description of the research.
6. For subjects whose native language is not English, informed consent must be obtained in a language that is understandable to the subject (or the subject's legally authorized representative). In accordance with this policy, the IRB requires that informed consent discussions include a reliable interpreter when the prospective subject does not understand the language of the person who is obtaining consent.
7. The informed consent process may not include any exculpatory language through which the subject is made to waive, or appear to waive any of the subject's legal rights or through which the investigator, the sponsor, the Organization or University of Virginia employees or agents are released from liability for negligence, or appear to be so released.
8. The investigator is responsible for ensuring that each prospective subject is adequately informed about all aspects of the research and understands the information provided.

11.4 Determining a potential adult subject's ability to consent to research

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

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

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

See Section 12.8 for further discussion regarding adults who cannot consent for themselves.

The decision-making capacity of a potential research subject should be evaluated when there are reasons to believe that the subject may not be capable of making voluntary and informed decisions about research participation.

The investigator and research staff must have adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and informed consent or assent. The IRB will evaluate whether the proposed plan to assess capacity to consent is adequate including consideration of state and local law and organizational policy.

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

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

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

Whenever the participants have the capacity to give consent (as determined by qualified professionals), informed consent should be obtained and document in accordance with Section 11.6 above. When participants lack the capacity to give consent, investigators may obtain consent from the legally authorized representative of a subject as described in Section 12.8.

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

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

11.5 Basic Elements of Informed Consent

To be valid, the consent process must provide the following basic elements of information to potential subjects:

1. A statement that the **study involves research**, an explanation of the **purposes** of the research and the **expected duration** of the subject's participation, a description of the **procedures** to be followed, and identification of any **procedures which are experimental**;
2. A description of any reasonably foreseeable **risks** or discomforts to the subject;

3. A description of any **benefits** to the subject or to others which may reasonably be expected from the research;
4. A disclosure of appropriate **alternative procedures** or courses of treatment, if any, that might be advantageous to the subject;
5. A statement describing the extent, if any, to which **confidentiality** of records identifying the subject must be maintained;
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
7. An **explanation of whom to contact** for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;
8. A statement that participation is **voluntary**, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled;
9. For **FDA-regulated studies**, a statement that notes the possibility that the Food and Drug Administration may inspect the records;
10. For "applicable" **FDA-regulated clinical trials**, the following statement must be included verbatim:

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

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

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

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

4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject;
6. The approximate number of subjects involved in the study.

11.6 Documentation of Informed Consent

Except as provided in Section 11.10 of this document, informed consent must be documented by the use of a written consent form approved by the IRB.

1. Informed consent is documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. The person obtaining consent will also sign the consent form for greater than minimal risk studies.
2. A copy of the signed and dated consent form must be given to the person signing the form. The investigator should retain the signed original in the research records.
3. The consent form may be either of the following:
 - a. A written consent document that embodies the basic and required additional elements of informed consent. The consent form may be read to the subject or the subject's legally authorized representative, but the subject or representative must be given adequate opportunity to read it before it is signed; or
 - b. A short form written consent document stating that the elements of informed consent have been presented orally to the subject or the subject's legally authorized representative, including required disclosures when the research involves private identifiable information or identifiable biospecimens.

When this method is used:

- i. The oral presentation and the short form written document should be in a language understandable to the subject; and
- ii. There must be a witness to the oral presentation; and
- iii. The IRB must approve a written summary of what is to be said to the subject (the approved full consent document may serve as this summary); and
- iv. The short form document is signed by the subject;
- v. The witness must sign both the short form and a copy of the summary; and
- vi. The person actually obtaining consent must sign a copy of the summary; and
- vii. A copy of the summary must be given to the subject or representative, in addition to a copy of the short form.

When this procedure is used with subjects who do not speak, or read, English, or have limited proficiency in oral or written English, (i) the oral presentation and

the short form written document should be in a language understandable to the subject; (ii) the IRB-approved English language informed consent document may serve as the summary; and (iii) the witness should be fluent in both English and the language of the subject. When the person obtaining consent is assisted by an interpreter, the interpreter may serve as the witness.

The IRB must receive all foreign language versions of the short form document as a condition of approval. Expedited review of these versions is acceptable if the protocol/research plan, the full English language informed consent document, and the English version of the short form document have already been approved by the convened IRB.

11.7 Special Consent Circumstances

11.7.1 Enrollment of persons with limited English-language proficiency

1. **Expected enrollment:** In some studies, the investigator may be able to anticipate enrollment of persons who do not speak or read, or have limited proficiency in, oral or written English. When the target subject population includes such persons or the investigator and/or the IRB otherwise anticipates that consent will be conducted in a language other than English, the IRB requires a translated consent document, and other subject materials, to be prepared. In order to ensure that translated documents are accurate, the IRB may choose to require a certified translation, to have an independent back-translation or to have a review of the translated documents by an IRB member or other person who is fluent in that language.
2. When non-English speaking subjects enroll, they and a witness sign the translated consent document. The **subjects are given a copy of the signed translated consent document.**
3. **Unexpected enrollment:** If a person who does not speak or read, or has limited proficiency in, English presents for possible enrollment, an IRB-approved translated version of the written consent may not be available for use. Investigators should carefully consider the ethical and legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented during the consent process or in subsequent discussions, his/her consent may not be informed, and therefore, not effective.

If an investigator decides to enroll a subject into a study for which there is not an extant IRB-approved consent document in the prospective subject's language, the investigator must receive IRB approval to follow the procedures for a "short form" written consent in as described in Section 11.6.

4. **Use of interpreters in the consent process:** Unless the person obtaining consent is fluent in the prospective subject's language, an interpreter will be necessary to

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

11.7.2 Braille consent

For blind subjects who read Braille, the IRB may approve a consent document prepared in Braille. In order to assure itself that a Braille consent document is accurate, the IRB may require a transcription into print text or review of the document by an IRB member or other person who reads Braille. If possible, the subject will sign the Braille consent; otherwise oral consent will be obtained, witnessed and documented as described under "Oral Consent" (see Section 11.7.4).

11.7.3 Consenting in American Sign Language (ASL)

For deaf subjects who are fluent in ASL, the IRB may approve a consent process using ASL and the IRB-approved written consent form. When this process is approved, the individual authorized to consent prospective subjects must use a certified interpreter fluent in ASL to conduct the consent process and the documentation of the consent process must conform to the requirements set forth in Section 11.6.

11.7.4 Oral Consent

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

For research that is no more than minimal risk, documentation of consent may be waived according to the criteria in Section 11.9.

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

the subject and, whenever possible, these documents should be provided to the subject on audio or video-tape.

11.7.5 Consent when a Minor becomes an Adult

Individuals enrolled as children with parental or guardian consent must be re-consented when they become adults (e.g. reach the legal Age of Majority in the state where the research is being conducted) unless an IRB determines that a waiver of consent can be granted.

11.8 Subject Withdrawal or Termination

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

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

- For FDA-regulated clinical trials, when a subject withdraws from a study, the data collected on the subject to the point of withdrawal remain part of the study database and may not be removed. The consent document cannot give the subject the option of having data removed.
- For research not subject to FDA regulations, the investigator should inform subjects whether the investigator intends to either: (1) retain and analyze already collected data relating to the subject up to the time of subject withdrawal; or (2) honor a research subject's request that the investigator destroy the subject's data or that the investigator exclude the subject's data from any analysis.

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

If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up as described in the previous paragraph, the investigator must obtain the subject's

informed consent for this limited participation in the study (assuming such a situation was not described in the original consent document). IRB approval of consent documents for these purposes would be required.

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

11.9 Waiver of Informed Consent

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

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

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

- (a) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
 - 1. Public benefit or service programs;
 - 2. Procedures for obtaining benefits or services under those programs;
 - 3. Possible changes in or alternatives to those programs or procedures; or
 - 4. Possible changes in methods or levels of payment for benefits or services under those programs; and,
- (b) The research could not practicably be carried out without the waiver or alteration.

FDA regulations do not provide for waivers of informed consent except in certain emergency situations. Additionally, waivers of consent are not permissible for federally-funded research using Newborn Blood Spots.

11.10 Waiver of Documentation of Informed Consent

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

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

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

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

or

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

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

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

11.11 Waiver of Informed Consent for Planned Emergency Research

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

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

The Secretary of Health and Human Services (DHHS) has implemented an Emergency Research Consent Waiver under *45 CFR 46.101(i)* with provisions equivalent to those of the FDA with the exception of the requirements specified in Sections 11.11.2.1 and 11.11.2.2 below. The DHHS waiver is not applicable to research involving prisoners, pregnant women, fetuses, or in vitro fertilization.

An exception from consent in emergency medicine research is prohibited unless the Secretary of Defense approves a waiver of the advance informed consent provision of 10 USC 980.

11.11.1 Definitions

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

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

11.11.2 Procedures

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

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

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give their informed consent as a result of their medical condition;

(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;

(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

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

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

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

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

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

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

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

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

(iv) Establishment of an independent data monitoring committee to exercise oversight of the research; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's

participation in the research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

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

11.11.2.1 FDA-regulated Planned Emergency Research

- 1) A licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation must concur that the conditions described in Section 11.11.2 are satisfied.
- 2) Studies involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies that such studies may include subjects who are unable to consent. The submission of those studies in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35.
- 3) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided in the regulations or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.
- 4) The IRB determinations and documentation required in Section 11.11.2 and paragraph 3 above are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 56.115(b).

11.11.2.2 Planned Emergency Research Not Subject to FDA Regulations

1) The IRB responsible for the review, approval, and continuing review of the research has approved both the research and a waiver of informed consent and has (i) found and documented that the research *is not subject* to regulations codified by the FDA at 21 CFR Part 50, and (ii) found and documented **and** reported to the OHRP that the conditions required Section 11.11.2 have been met relative to the research

11.12 Following the ICH-GCP (E6) Guidelines

When following the ICH-GCP (E6) guidelines the following applies:

- The IRB determines that the following consent disclosures are included:
 - o The approval or favorable opinion by the IRB.
 - o The probability for random assignment to each treatment.
 - o The subject's responsibilities.
 - o The alternative procedures or treatment that might be available to the subject, and their important potential benefits and risks.
 - o When applicable, the reasonably foreseeable risks or inconveniences to an embryo, fetus, or nursing infant.
 - o The important potential benefits and risks of the alternative procedures or courses of treatment that may be available to the subject.
 - o When there is no intended clinical benefit to the subject, the subject should be made aware of this.
 - o A statement that the monitors, the auditors, the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally authorized representative is authorizing such access.
 - o A statement that if the results of the trial are published, the subject's identity will remain confidential.
- Documentation of the consent process include:
 - o Prior to a subject's participation in the trial, the written consent document should be signed and personally dated by the subject or by the subject's legally acceptable representative.
 - o Prior to a subject's participation in the trial, the written consent document should be signed and personally dated by the person who conducted the informed consent discussion.
 - o If a subject is unable to read or if a legally acceptable 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 subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject'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 subject or the subject's legally acceptable representative, and that consent was freely given by the subject or the subject's legally acceptable representative.

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

12 Vulnerable Subjects in Research

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

The following procedures describe the requirements for involving vulnerable participants in research under the auspices of the University of Virginia.

12.1 Definitions

Coercion. Coercion occurs when a person is compelled to involuntarily behave in a certain way by use of overt or implicit threat of harm, intimidation, or other form of pressure or force. Coercion also occurs when potential subjects perceive pressure or force to participate. For example, an investigator might tell a potential subject that failure to participate will result in the loss of salary or other benefits, or a lowered course grade; or these potential harms may be perceived or lose access to needed health services.

Undue Influence. Undue influence occurs when a person takes advantage of a position of power by offering excessive or inappropriate rewards for compliance, or, whether intended or not, the person in the position of power undermines the potential subject's freedom of choice. For example, an investigator might tell a potential subject that the decision to participate will result in a job promotion or better course grade; or the person may perceive s/he lacks the freedom of choice.

Children. Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

The definition of "children" also takes into account the particular treatments or procedures involved in the proposed research; for example, minors may legally consent to certain medical treatments under Virginia law (see below), and so if the involvement of human subjects in a proposed research activity consists of these treatments, then they may be considered as adults for that purpose. If a proposed activity includes something for which the subject has not yet reached the legal age of consent, however, that person must be considered a child.

Under Virginia law, minors are deemed to be adults for purposes of consenting to the following:

1. venereal disease or other reportable infectious or contagious disease
2. birth control, pregnancy or family planning except for the purposes of sexual sterilization;
3. outpatient care, treatment or rehabilitation for substance abuse;
4. outpatient care, treatment or rehabilitation for mental illness or emotional disturbance;
5. for pregnant minors, consent for both herself and her child to surgical and medical treatment relating to the delivery of her child, during the hospital admission for delivery; thereafter, consent for any treatment for the child, but not for herself unless it falls into categories 1-4 above.
6. any treatment for a minor who is or has been married, except sexual sterilization. Nontherapeutic sexual sterilization requires a court order.

Guardian. A guardian is an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.

Under Virginia law, there is no single Virginia statute with a comprehensive definition of "guardian" or "guardianship" regarding minors. The crucial common denominator for guardianship is the existence of a court order appointing a guardian of the child.

The court-ordered status of guardian of the child gives the authority to make medical decisions. (A guardian of the estate of a child is appointed to manage the property of a minor, and does not have rights to make medical decisions.)

Virginia law also provides for medical decision-making when parental rights have not been terminated but custody has been transferred to another person or entity. See <http://law.lis.virginia.gov/vacode/title54.1/chapter29/section54.1-2969/>.

Medical decision-making authority is conferred:

1. Upon local directors of departments of social services or their designees regarding minors in their custody.
2. Upon the Director of the Department of Corrections or the Director of the Department of Juvenile Justice or their designees regarding minors in their custody.
3. Upon the principal executive officers of state institutions regarding the wards of such institutions.
4. Upon the executive officer of any other agency legally qualified to receive minors separated from their parents or guardians, regarding any minor of whom they have custody.

Research conducted outside Virginia:

The IRB will consult with the Office of University Counsel to determine who under applicable law is authorized to consent on behalf of a child to the treatments or procedures in the applicable research stud[ies].

Fetus. A fetus means the product of conception from implantation until delivery.

Dead fetus. A fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

Delivery. A delivery is a complete separation of the fetus from the woman by expulsion or extraction or any other means.

Neonate. A neonate is a newborn.

Viable. As it pertains to the neonate, viable means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.

Nonviable neonate. A nonviable neonate means a neonate after delivery that, although living, is not viable.

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

Prisoner. A prisoner is any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

12.2 Involvement of Vulnerable Populations

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

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

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

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

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

In its FWA, the University of Virginia has opted to voluntarily apply the Common Rule (i.e., Subpart A) to all of its human subject research including all non-federally funded research. Subparts B, C, and D of 45 CFR 46 are applied to all research regardless of funding with the exception of Subpart B which will not be applied to social, behavioral, educational and non-therapeutic medical research.

The individual sections describe how the subparts apply specifically to DHHS-funded research.

12.3 Responsibilities

1. The investigator is responsible for identifying the potential for enrolling vulnerable subjects in the research proposal, including the possible inclusion of subjects who are at risk for impaired decisional capacity, and who are being asked to participate in a research study with greater than minimal risk.
2. The IRB shall include representation, either as members or through the use of consultants, of individual(s) who are knowledgeable about or experienced working with the vulnerable populations involved in the research proposal under review.
3. The IRB reviews the investigator's justifications for including vulnerable populations in the research to assess appropriateness for inclusion in the research proposal.
4. The IRB must ensure that appropriate additional safeguards have been included in each study to protect the rights and welfare of vulnerable subjects at the time of initial review of the research proposal.
5. Information reviewed as part of the continuing review process should include the number of participants considered to be members of specific vulnerable populations.

12.4 Procedures

Initial Review of Research Proposal:

1. The investigator identifies the potential to enroll vulnerable subjects in the proposed research at initial review and provides the justification for their inclusion in the study.
2. The investigator describes safeguards to protect the subject's rights and welfare in the research proposal.
3. The IRB evaluates the proposed safeguards, including, if applicable, the proposed plan for obtaining consent from legally authorized representatives and the plans for assent of children and adults unable to provide consent.
4. The IRB evaluates the research to determine the need for additional protections and considers, if appropriate, the use of a data and safety monitoring board, consent monitor, or research subject advocate.

Continuing Review and Monitoring. At Continuing Review the investigator should identify the number and categories of vulnerable subjects enrolled and any problems that arose relevant to their rights and welfare.

12.5 Research Involving Pregnant Women, Human Fetuses and Neonates

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

12.5.1 Research Involving Pregnant Women or Fetuses

12.5.1.1 Research Not Conducted or Supported by DHHS

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

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

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus;
3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent;
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children (as defined in Section 12.1) who are pregnant, assent and permission are obtained in accord with the requirements of state law and the IRB;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. The IRB may allow individuals whose normal responsibilities include determining the viability of fetuses to be engaged in the research, if their involvement in the determination of viability for an individual fetus cannot be avoided. Confirmation of the determination regarding viability will be sought from a qualified individual who is not otherwise engaged in the research whenever possible prior to beginning the research. The opinion of the independent qualified individual will be documented and made available upon request to the IRB or HRPP representative. When advance confirmation is not possible, the investigator will obtain it as soon as s/he can after enrollment, but in all cases within 3 business days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within 5 business days.

12.5.1.2 Research Conducted or Supported by DHHS

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

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

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent.
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

6. Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children (as defined in Section 12.1) who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 12.7.2;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

12.5.2 Research Involving Neonates of Uncertain Viability or Nonviable Neonates

12.5.2.1 Research Not Conducted or Supported by DHHS

Neonates of uncertain viability and nonviable neonates may be involved in research **involving more than minimal risk** if all of the following conditions are met:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
3. The IRB may allow individuals whose normal responsibilities include determining the viability of neonates to be engaged in the research, if their involvement in the determination of viability for an individual neonate cannot be avoided. In such cases, confirmation of the determination regarding viability must be made by a qualified individual who is not otherwise engaged in the research whenever possible prior to beginning the research. The opinion of the independent qualified individual will be documented and made available upon request to the IRB or HRPP representative. When advance confirmation is not possible, the investigator will obtain it as soon as s/he can after enrollment, but in all cases within 3 business days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within 5 business days.
4. The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below in this section) have been met as applicable.

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

The IRB determines that:

1. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
2. The purpose of the research is the development of important knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
3. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with the provisions of permission and assent, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

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

1. Vital functions of the neonate will not be artificially maintained;
2. The research will not terminate the heartbeat or respiration of the neonate;
3. There will be no added risk to the neonate resulting from the research;
4. The purpose of the research is the development of important knowledge that cannot be obtained by other means; and
5. The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply.

However, if either parent is unable to consent because of unavailability, 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.

12.5.2.2 Research Conducted or Supported by DHHS

Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.
4. The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below in this section) have been met as applicable.

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

The IRB determines that:

1. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
2. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
3. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with the provisions of permission and assent, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

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

1. Vital functions of the neonate will not be artificially maintained;
2. The research will not terminate the heartbeat or respiration of the neonate;
3. There will be no added risk to the neonate resulting from the research;
4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
5. The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply.

However, if either parent is unable to consent because of unavailability or incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph.

12.5.3 Viable Neonates

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

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

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

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

12.5.5 Research Not Otherwise Approvable

12.5.5.1 Research Not Conducted or Supported by DHHS

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

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

12.5.5.2 Research Conducted or Supported by DHHS

DHHS conducted or supported research that falls in this category must be approved by the Secretary of Health and Human Services. If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and the

research is not approvable under the above provisions, then the research will be sent to OHRP for DHHS review.

12.6 Research Involving Prisoners

The following applies to all research involving prisoners, regardless of funding source. The requirements in this section are consistent with Subpart C of 45 CFR 46, which applies to DHHS-funded or supported research.

12.6.1 Applicability

This policy applies to all biomedical and behavioral research conducted under the auspices of University of Virginia involving prisoners as subjects. Even though the IRB may approve a research study involving prisoners as subjects according to this policy, investigators are also subject to the Administrative Regulations of the Virginia Department of Corrections, at Agency 15, Chapter 26. <http://lis.virginia.gov/000/reg/TOC06015.HTM#C0026>, regarding research conducted in a Department of Corrections unit, and any other applicable State or local law. [45 CFR 46.301]

12.6.2 Minimal Risk

Minimal risk, in studies involving prisoners, means the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

12.6.3 Composition of the IRB

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

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

12.6.4 Review of Research Involving Prisoners

1. Initial Review

- a. The prisoner representative must review research involving prisoners, focusing on the requirements in Subpart C.
 - b. The prisoner representative must receive all review materials pertaining to the research (same as primary reviewer).
 - c. The prisoner representative must be present at a convened meeting when the research involving prisoners is reviewed. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved. The prisoner representative may attend the meeting by phone, video-conference, or webinar, as long as the representative is able to participate in the meeting as if they were present in person at the meeting.
2. Modifications.
- a. Minor modifications to research may be reviewed using the expedited procedure described below using either of the two procedures described based on the type of modification.
 - b. Modifications involving more than a minor change reviewed by the convened IRB must use the same procedures for initial review including the responsibility of the prisoner representative to review the modification and participate in the meeting (as described above).
3. Continuing review. Continuing review must use the same procedures for initial review including the responsibility of the prisoner representative to review the continuing review materials and participate in the meeting (as described above).
4. Expedited Review
- a. Research involving interaction with prisoners may be reviewed by the expedited procedure, if a determination is made that the research involves no greater than minimal risk for the prison population being studied and the research falls within the categories of research eligible for expedited review. Whenever possible, the prisoner representative will be consulted to verify that they agree that the research is minimal risk and to conduct (if designated by the IRB Chair as an expedited reviewer) or participate in the expedited review as a consultant. Review of modifications and continuing review will follow the initial review using the expedited procedure.
 - b. Research that does not involve interaction with prisoners (e.g., existing data, records review, etc.) may be reviewed by the expedited procedure, if a determination is made that the research involves no greater than minimal risk for the prison population being studied. Review by a prisoner representative is not required. The prisoner representative may review the research as a reviewer (if designated by the IRB Chair as an expedited reviewer) or consultant. Review of modifications and continuing review will follow these same procedures.

12.6.5 Incarceration of Enrolled Subjects

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

1. Confirm that the participant meets the definition of a prisoner.
2. Consult with the investigator to determine if it is in the best interests of the participant to continue participation in the study, in part or in full, and if so, if there are specific study activities which are in the best interests of the subject and should continue until the IRB is able to review the research study under Subpart C.
3. If the participant should continue, one of two options are available:
 - a. Keep the participant enrolled in the study and review the research under Subpart C. If some of the requirements of Subpart C cannot be met or are not applicable (e.g., procedures for the selection of subjects within the prison), but it is in the best interests of the participant to remain in the study, keep the participant enrolled and inform OHRP of the decision along with the justification.
 - b. Remove the participant from the study and keep the participant on the study intervention under an alternate mechanism such as compassionate use, off label use, etc.
4. If a participant is incarcerated temporarily while enrolled in a study:
 - a. If the temporary incarceration has no effect on the study (i.e., there is no need for study activities to take place during the temporary incarceration), keep the participant enrolled.
 - b. If the temporary incarceration has an effect on the study, follow the above guidance.

12.6.6 Additional Duties of the IRB

In addition to all other responsibilities prescribed for IRB in other sections of this manual, the IRB will review research involving prisoners and approve such research only if it finds that:

- The research falls into one of the following **permitted categories** [45 CFR 46.306(a)(2)]:
 - Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
 - Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
 - Research on conditions particularly affecting prisoners as a class (for example, research on diseases or social and psychological problems much more prevalent in prisons) provided that the study may proceed only after the DHHS Secretary

has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research;

- Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols/research plans approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the DHHS Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research
- Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
- The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
- Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the investigator provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
- The information is presented in language which is understandable to the subject population;
- Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
- Where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing subjects of this fact.

12.6.7 Certification to DHHS

Under 45 CFR 46.305(c), the institution responsible for conducting research involving prisoners that is conducted or supported by DHHS shall certify to the Secretary (through OHRP) that the IRB has made the seven findings required under 45 CFR 46.305(a) and receive OHRP authorization prior to initiating any research involving prisoners. Certifications, and requests for DHHS Secretarial consultation, do not need to be submitted to OHRP for research not

conducted or supported by DHHS, regardless of whether the institution has chosen to extend the applicability of its FWA and Subparts B, C, and D to all research.

For all DHHS conducted or supported research, University of Virginia will send to OHRP a certification letter to this effect, which will also include the name and address of the institution and specifically identify the research study in question and any relevant DHHS grant application or protocol/research plan. DHHS conducted or supported research involving prisoners as subjects may not proceed until OHRP issues its authorization in writing to University of Virginia on behalf of the Secretary under 45 CFR 46.306(a)(2).

Under its authority at 45 CFR 46.115(b), OHRP requires that the institution responsible for the conduct of the proposed research also submit to OHRP a copy of the research proposal so that OHRP can determine whether the proposed research involves one of the categories of research permissible under 45 CFR 46.306(a)(2), and if so, which one.

The term “research proposal” includes:

- The IRB-approved protocol/research plan; any relevant DHHS grant application or proposal;
- Any IRB application forms required by the IRB;
- And any other information requested or required by the IRB to be considered during initial IRB review.

OHRP also encourages the organization to include the following information in its prisoner research certification letter to facilitate processing:

- The OHRP Federalwide Assurance (FWA) number;
- The IRB registration number for the designated IRB; and
- The date(s) of IRB meeting(s) in which the study was considered, including a brief chronology that encompasses:
 - The date of initial IRB review; and
 - The date of subpart C review, if not done at the time of initial IRB review.

12.6.8 Waiver for Epidemiology Research

The DHHS Secretarial waiver for certain epidemiological research conducted or supported by DHHS functions as a fifth category of permissible research [68 FR 36929]. The criteria for this category are that the research must have as its sole purpose (i) to describe the prevalence or incidence of a disease by identifying all cases, or (ii) to study potential risk factor associations for a disease. The organization still must review the research under subpart C and certify to OHRP that an appropriately constituted IRB has reviewed the proposal and made all other required findings under DHHS regulations at 45 CFR 46.305(a) and receive OHRP authorization prior to initiating any research involving prisoners. All of the other requirements of subpart C apply to research in this category.

12.7 Research Involving Children

The following applies to all research involving children, regardless of funding source. The requirements in this section are consistent with Subpart D of 45 CFR 46, which applies to DHHS-funded research and Subpart D of 21 CFR 50, which applies to FDA-regulated research involving children.

12.7.1 Allowable Categories

In addition to the IRB's normal duties, research involving children must be reviewed by the IRB to determine if it fits within and is permissible under one or more federally-defined categories (OHRP/FDA). Each procedure or intervention that the child will undergo for the research must be taken into consideration, and, if the research includes more than one study group assignment (e.g., placebo vs. active, investigational agent vs. comparator) the category determination must be made for each group assignment. In other words, a component analysis must be conducted by the IRB. The categories are as follows:

1. **[45 CFR 46.404/21 CFR 50.51] Research/Clinical Investigations not involving greater than minimal risk.** Research determined to not involve greater than minimal risk to child subjects may be approved by the IRB only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in Section 12.7.2.
2. **[45 CFR 46.405/21 CFR 50.52] Research/Clinical Investigations involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.** Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may be approved by the IRB only if the IRB finds and documents that:
 - The risk is justified by the anticipated benefit to the subjects;
 - The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative options; and
 - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 12.7.2.
3. **[45 CFR 46.406/21 CFR 50.53] Research/Clinical Investigations involving greater than minimal risk and no prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition.** Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, may be approved by the IRB only if the IRB finds and documents that:

- The risk represents a minor increase over minimal risk;
 - The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
 - The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
 - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 12.7.2.
4. **[45 CFR 46.407/21 CFR 50.54] Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children.** When the IRB does not believe that the research meets the requirements of any of the above categories, and the IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the IRB shall refer the research for further review as follows:
- HHS conducted or supported research in this category will be referred for review by the Secretary of Health and Human Services. However, before doing so the IRB must determine that the proposed research also meets all of the requirements of the Common Rule.
 - FDA-regulated research in this category will be referred for review by the Commissioner of Food and Drugs.
 - For research that is not DHHS conducted or supported and not FDA-regulated, the IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on either:
 - That the research in fact satisfies the conditions of the previous categories, as applicable; or
 - The following:
 - The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
 - The research will be conducted in accord with sound ethical principles; and
 - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 12.7.2.

12.7.2 Parental Permission and Assent

12.7.2.1 Parental Permission

The IRB must determine that adequate provisions have been made for soliciting the permission of each child's parent or guardian.

Parents or guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary, as described in Section 11.5.

The IRB may find that the permission of one parent is sufficient for research to be conducted under Categories 1 [45 CFR 46.404/21 CFR 50.51] & 2 [45 CFR 46.405/21 CFR 50.52] above. The IRB's determination of whether permission must be obtained from one or both parents will be documented in the reviewer's notes when a study receives expedited review, and in meeting minutes when reviewed by the convened committee.

Permission from both parents is required for research to be conducted under Categories 3 [45 CFR 46.406/21 CFR 50.53] & 4 [45 CFR 46.407/21 CFR 50.54] above unless

1. One parent is deceased, unknown, incompetent, or not reasonably available; or
2. When only one parent has legal responsibility for the care and custody of the child.

For research not covered by the FDA regulation, the IRB may waive the requirement for obtaining permission from a parent or legal guardian if:

- The research meets the provisions for waiver in Section 11.9 or
- If the IRB determines that the research is designed to study conditions in children or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children) provided that an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal, State, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol/research plan, the risk and anticipated benefit to the research subjects, and the child's age, maturity, status, and condition.

Parental permission may not be waived for research covered by the FDA regulations.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by Section 11.6.

12.7.2.2 Assent from Children

The IRB is responsible for determining that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. This judgment may be made for all children to be involved in the study, or for each child, as the IRB deems appropriate.

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 where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accordance with the applicable regulations. It is important to note that the FDA regulations do permit the IRB to waive the assent requirement if it finds and documents that:

1. The clinical investigation involves no more than minimal risk to the subjects;
2. The waiver will not adversely affect the rights and welfare of the subjects;
3. The clinical investigation could not practicably be carried out without the waiver; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Because “assent” means a child’s affirmative agreement to participate in research, the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way.

The IRB should take into account the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects. For research activities involving adolescents whose capacity to understand resembles that of adults, the assent procedure should likewise include information similar to what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity, but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (for example, what the experience will be, how long it will take, whether it might involve any pain or discomfort). The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve.

Parents and children will not always agree on whether the child should participate in research. Where the IRB has indicated that the assent of the child is required in order for him or her to be enrolled in the study, dissent from the child overrides permission from a parent. Similarly, a child typically cannot decide to be in research over the objections of a parent. There are individual exceptions to these guidelines but in general, children should not be forced to be research subjects, even when permission has been given by their parents.

Documentation of Assent

When the IRB determines that assent is required, it also is also responsible for determining whether and how assent must be documented. When the research targets the very young child or children unable or with limited capacity to read or write, an oral presentation accompanied perhaps by some pictures with documentation of assent by the person obtaining assent in a research note is likely more appropriate than providing the child a form to sign. In this case, the investigator should provide the IRB with a proposed script and any materials that they intend to use in explaining the research.

When the research targets children who are likely able to read and write, investigators should propose a process and form that is age appropriate and study specific, taking into account the typical child's experience and level of understanding, and composing a document that treats the child respectfully and conveys the essential information about the study. The assent form should:

1. Tell why the research is being conducted;
2. Describe what will happen and for how long or how often;
3. Say it's up to the child to participate and that it's okay to say no;
4. Explain if it will hurt and if so for how long and how often;
5. Say what the child's other choices are;
6. Describe any good things that might happen;
7. Say whether there is any compensation for participating; and
8. Ask for questions.

Whenever possible, the document should be limited to one page. Illustrations might be helpful, and larger type and other age appropriate improvements are encouraged when they have the potential to enhance comprehension. Studies involving older children or adolescents should include more information and may use more complex language.

12.7.2.3 Children Who are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406/21 CFR 50.53 or 45 CFR 46.407/21 CFR 50.54 (Categories 3 & 4 in Section 12.7.1), **only if such research is:**

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

If the research meets the condition(s) above, an advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in *loco parentis*.

The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

12.8 Adults with Impaired Decision Making Capacity

The requirements in this section apply to all research involving adults who cannot provide consent or with impaired decision-making capacity regardless of funding source.

Research involving subjects without the ability to provide consent or with impaired decision-making capacity should only be conducted when the aims of the research cannot reasonably be achieved without their participation. Participation of such subjects in research cannot be justified solely on their availability or the convenience for the investigator.

When an investigator seeks to include such subjects in research, they must disclose this to the IRB and provide justification for why inclusion is necessary. If capacity to consent is questionable, or may fluctuate, investigators should include provisions for determining capacity to provide informed consent (see definitions under 11.1 and Section 11.4), and, if appropriate for evaluating capacity during participation. If the research includes patients, the investigators should consult Virginia State Code Sec 54.1-2983.2 and for patients of the UVA Health System, refer to Medical Center Policy # 0024. When capacity to consent may diminish, the procedures should include, when possible and appropriate, designation of a legally-authorized authorized representative (LAR), inclusion of the future LAR in the initial consent discussion and process, and memorialization of the participant's wishes regarding the research in writing. When the research includes subjects likely to regain capacity to consent, the investigator should include provisions to inform the subject regarding their participation and to seek consent for ongoing participation, if applicable.

When the IRB reviews research involving greater than minimal risk and the proposed subject population includes adults who cannot provide consent, may have impaired capacity to provide consent, or whose capacity can be expected to fluctuate over time, the IRB review process will include at least one member, or a consultant, who is experienced with or otherwise knowledgeable about the population.

In evaluating research, the IRB must be able to determine that the risks to subjects are reasonable not only in relation to any benefits, but also in relation to the importance of the knowledge that may reasonably be expected to result. In considering the risks of research involving subjects unable to provide informed consent or with diminished capacity to do so, the IRB should consider whether any components of the research involve risks that are greater for participants with diminished capacity. For example, the population might experience increased sensitivity or discomfort to certain stimuli or may not be able to verbalize or otherwise demonstrate when they are experiencing discomfort or pain.

Research conducted by the University of Virginia will not allow the use of an LAR for non-therapeutic research that is more than a slight increase over minimal risk.

If the study is following ICH-GCP (E6) Guidelines and when adults are unable to give consent the IRB will determine:

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

13 FDA-Regulated Research

FDA regulations apply to research that involves a FDA-regulated *test article* in a *clinical investigation* involving *human subjects* as defined by the FDA regulations. For FDA-regulated research, the IRB must apply the FDA regulations at 21 CFR 50 and 21 CFR 56. If required by organizational policy or a FWA, 45 CFR 46 must also be applied.

Clinical trials with investigational drugs must be conducted according to FDA's IND regulations, 21 CFR Part 312, and other applicable FDA regulations. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations, 21 CFR Part 812, and other applicable FDA regulations.

The following procedures describe the review of FDA-regulated research conducted under the auspices of University of Virginia.

13.1 Definitions

Biologic. Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other technologies. In general, the term "drugs" includes therapeutic biological products.

Dietary Supplement. A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains a dietary ingredient. The dietary ingredients in these

products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. See section 201(ff) of the FD&C Act [21 U.S.C. 321(ff)].

Investigational Drug. Investigational *or* experimental drugs are new drugs that have not yet been approved by the FDA or approved drugs that are being studied in a clinical investigation.

Investigational Device. Investigational device means a device (including a transitional device) that is the object of an investigation. Investigation, as it pertains to devices, means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

IND. IND means an investigational new drug application in accordance with 21 CFR Part 312.

IDE. IDE means an investigational device exemption in accordance with 21 CFR 812.

In Vitro Diagnostic Product (IVD). In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. [21 CFR 809.3(a)]

Emergency Use. Emergency use is defined as the use of an investigational product with a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. [21CFR 56.102(d)]

Significant Risk (SR) Device. Significant risk device means an investigational device that:

- (1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- (2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- (3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- (4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Non-Significant Risk (NSR) Device. A non-significant risk device is an investigational device that does not meet the definition of a significant risk device.

Humanitarian Use Device (HUD). A Humanitarian Use Device is a device intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.

13.2 FDA Exemptions

The following categories of clinical investigations are exempt from the requirements of FDA regulations for IRB review:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [21 CFR §56.104(c)]
2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR §56.104(d)]

13.3 Procedures

- A. At initial submission, the investigator must indicate whether the research involves a test article and is a clinical investigation involving human subjects on the application form. The investigator may use information provided in the IRB application to assist in making this determination.
- B. During the pre-review process, an IRB staff member will confirm whether FDA regulations are applicable using the Administrator Reviewer Checklist. If FDA regulations apply and the research is not exempt, the IRB staff member will indicate on the agenda that the study is FDA-regulated.
- C. If the study involves investigational drugs and is industry sponsored and required by the sponsor, the University of Virginia will follow ICH-GCP E6 to the extent it is consistent with FDA regulations.

13.4 Investigator Responsibilities

The investigator holds additional responsibilities when conducting a clinical trial evaluating FDA-regulated drugs, devices, and other articles. These responsibilities include, but are not limited to, the following:

1. The investigator is responsible for ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs (including biological products) or agreement for clinical investigations of medical devices, the investigational plan and other applicable regulations, and any requirements imposed by the IRB or FDA.
2. The investigator is responsible for personally conducting or supervising the investigation. When certain study-related tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks

are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

3. The investigator must maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (e.g., it can refer to an individual's CV on file and/or training conducted by the investigator/sponsor), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.
4. The investigator is responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial. This responsibility includes:
 - Informing subjects that the test articles is being used for investigational purposes and ensuring that the requirements relating to obtaining informed consent are met
 - Providing reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention
 - Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, or when specialized care is needed)
 - Adhering to the protocol/research plan so that study subjects are not exposed to unreasonable risks
 - As appropriate, informing the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and the subject agrees to the primary physician being informed
5. The investigator is responsible for reading and understanding the information in the investigator brochure or device risk information, including the potential risks and side effects of the drug or device.
6. The investigator is responsible for maintaining adequate and accurate records in accordance with FDA regulations and to making those records available for inspection by the FDA. These records include: correspondence with other investigators, the IRB, the sponsor, monitors, or the FDA; drug and device accountability records; case histories; consent forms; and documentation that consent was obtained prior to any participation in the study. Records must be obtained for a minimum of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such. Other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors may necessitate retention for a longer period of time.

7. The investigator is responsible for controlling drugs, biological products, and devices according to FDA regulations and the Controlled Substances Act, if applicable.
8. The investigator proposing the clinical investigation will be required to provide a plan to be evaluated by the IDS - that includes storage, security, and dispensing of the test article.
 - a. The investigator is responsible for investigational drug accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability. Such details will be provided in the submission and reviewed by the IDS for acceptability.
 - b. The investigator may delegate, as part of the submission, the responsibility detailed in 'a' above to the IDS.
 - c. All devices received for a study must be stored in a locked environment under secure control with limited access. Proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use, and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.
9. The investigator shall furnish all reports required by the sponsor of the research including adverse events, progress reports, safety reports, final reports, and financial disclosure reports.
10. The investigator will permit inspection of research records by the sponsor, sponsor representatives, HRPP and IRB representatives, the FDA, accrediting bodies, and any other agencies or individuals entitled to inspect such records under regulation, organizational policy, or contractual agreement.

13.5 Dietary Supplements

Research involving dietary supplements may or may not fall under FDA regulations. Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, a dietary supplement is not considered a drug and is not subject to the premarket approval requirements for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose). Whether a study falls under FDA oversight is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, FDA research regulations do not apply. However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, then FDA regulations do apply. Studies involving the ingestion of dietary supplements that are not subject to FDA oversight are still research, and therefore must be reviewed by the IRB.

Similarly, whether an IND is needed for a study evaluating a dietary supplement is determined by the intent of the study. If the study is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required. However, if the study is

intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required under part 312.

As with any research involving a test article, the investigator must supply the IRB with sufficient information to determine that the criteria for approval are satisfied and to determine or verify whether or not the research requires an IND. Applications should provide detail consistent with that expected on a drug protocol/research plan and consistent with the level of risk associated or anticipated with the research. At a minimum, the research plan should provide the following information regarding the supplement: Name, Manufacturer, Formulation, Dosage, Method/Route of Administration, Mechanism of Action, Known Drug Interactions, Risk Profile, IND number (or justification for why an IND is unnecessary), documentation of approval for use in humans, documentation or certification of Quality or Purity. As with drugs and devices there should be an accountability plan for the product describing where the product will be stored and how it will be dispensed, usage tracked, and disposal or return. If the study entails greater than minimal risk, a plan for Data and Safety Monitoring must be included.

13.6 Clinical Investigations of Drugs and Devices

13.6.1 IND/IDE Requirements

For studies evaluating the safety or effectiveness of medical devices or experiments using drugs, biologics, dietary supplements, and other compounds that may be considered a drug under FDA regulations, the investigator must indicate on the IRB application whether or not an IDE or IND is in place, and, if not, the basis for why an IDE or IND is not needed.

Documentation must be provided by the sponsor or the sponsor-investigator. Documentation of the IND/IDE could be a:

1. Industry sponsored study with IND/IDE number indicated on the protocol/research plan.
2. Letter/communication from FDA.
3. Letter/communication from industry sponsor.
4. Other document and/or communication verifying the IND/IDE.

For investigational devices, the study may be exempt from IDE requirements or, in the case of Non-significant Risk (NSR) device studies, follow abbreviated IDE requirements which do not require formal approval by the FDA. If a sponsor has identified a device study as exempt or NSR, then the investigator should include documentation with the submission providing the basis for exempt or NSR categorization. If the FDA has determined that the study is exempt or NSR, documentation of that determination must be provided.

The IRB will review the application and, based upon the documentation provided, determine: (1) that there is an approved IND/IDE in place, (2) that the FDA has determined that an IND is not required or that a device study is exempt or NSR, or, (3) if neither of the above, whether or not an IND is necessary, or that a device study is exempt or NSR, using the criteria below. The IRB cannot grant approval and research cannot begin, including recruiting, obtaining consent, and screening participants, until the IND/IDE status is determined, and, if necessary, an

approved IND or IDE is in place. . Please Note: An IND goes into effect 30 days after the FDA receives the IND, unless the sponsor receives earlier notice from the FDA.

13.6.1.1 IND Exemptions

For drugs, an IND is not necessary if the research falls in one of the following seven (7) categories:

1. The drug being used in the research is lawfully marketed in the United States and all of the following requirements are met:
 - a. The research is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug
 - b. In the case of a prescription drug, the research is not intended to support a significant change in the advertising for the product;
 - c. The research does not involve a route of administration, dose, subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
 - d. The research is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
 - e. The research is conducted in compliance with the requirements of 21 CFR 312.7 (i.e., the research is not intended to promote or commercialize the drug product); and
 - f. The research does not intend to invoke FDA regulations for planned emergency research [21 CFR 50.24].
2. The research only involves one or more of the following: (a) Blood grouping serum, (b) Reagent red blood cells or (c) Anti-human globulin;
3. For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and b) it is shipped in compliance with 312.160
4. A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.
5. Bioavailability or Bioequivalence (BA/BE) studies if all of the following conditions are met:
 - a. The drug product does not contain a new chemical entity [21 CFR 314.108], is not radioactively labeled, and is not cytotoxic;
 - b. The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product;
 - c. The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; and
 - d. The sponsor meets the requirements for retention of test article samples [21 CFR 320.31(d)(1)] and safety reporting [21 CFR 320.31(d)(3)].

6. Research using a radioactive drug or biological product if all of the following conditions are met:
 - a. It involves basic research not intended for immediate therapeutic, diagnostic, or similar purposes, or otherwise to determine the safety and efficacy of the product;
 - b. The use in humans is approved by a Radioactive Drug Research Committee (RDRC) that is composed and approved by FDA;
 - c. The dose to be administered is known not to cause any clinically detectable pharmacological effect in humans, and
 - d. The total amount of radiation to be administered as part of the study is the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and is within specified limits.
7. FDA practices enforcement discretion for research using cold isotopes of unapproved drugs if all of the following conditions are met:
 - a. The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry;
 - b. The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject;
 - c. The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies;
 - d. The quality of the cold isotope meets relevant quality standards; and
 - e. The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively].

13.6.1.2 IDE Exemptions

For clinical investigations of devices, an IDE is not necessary if:

1. The research involves a device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time;
2. The research involves a device other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence (a “501k” device);
3. The research involves a diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
 - a. Is noninvasive,
 - b. Does not require an invasive sampling procedure that presents significant risk,

- c. Does not by design or intention introduce energy into a subject, and
 - d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;
- 4. The research involves a device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;
- 5. The research involves a device intended solely for veterinary use;
- 6. The research involves a device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 812.5(c);
- 7. The research involves a custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

13.6.1.3 Significant and Non-Significant Risk Device Studies

A device study is a Non-Significant Risk (NSR) Device study if it is not IDE exempt and does not meet the definition of a Significant Risk (SR) Device study.

Under 21 CFR 812.3(m), an SR device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

If the FDA has already determined a study to be SR or NSR, documentation evidencing such should be provided to the IRB as described in Section 13.6.1. The FDA's determination is final and the IRB does not have to make the device risk determination.

Unless the device is determined to be exempt from IDE regulations or the FDA has already made a device risk determination for the study, the IRB will review studies that the sponsor or investigator have put forth as NSR at a convened meeting to determine if the device represents SR or NSR.

The sponsor or sponsor-investigator is responsible for providing the IRB with an explanation describing the basis for their initial determination of NSR and any other information that may help the IRB in evaluating the risk of the study (e.g., reports of prior investigations of the device).

The IRB will review the information provided by the sponsor and investigator including, but not limited to: the sponsor or investigator's NSR assessment, the description of the device, reports of prior investigations of the device (if applicable), the proposed investigational plan, and subject selection criteria.

The NSR/SR determination made by the IRB will be based on the proposed use of the device in the investigation, not on the device alone. The IRB will consider the nature of any harms that may result from use of the device, including potential harms from additional procedures subjects would need to undergo as part of the investigation (e.g., procedures for inserting, implanting, or deploying the device). The IRB may consult with the FDA or require the sponsor or investigator to obtain a determination from the FDA. The IRB will document the SR or NSR determination and the basis for it in the meeting minutes and provide the investigator, and sponsor when applicable, with the determination in writing.

Non-significant risk device studies do not require submission of an IDE application to the FDA but must be conducted in accordance with the abbreviated requirements of IDE regulations (21 CFR 812.2(b)). Under the abbreviated requirements, the following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under 812.20(a) that approval of an application is required:

- (1) An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor (or sponsor-investigator):
 - (i) Labels the device in accordance with 812.5;
 - (ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with an explanation of why the device is not a significant risk device, and maintains such approval;
 - (iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under 56.109(c).
 - (iv) Complies with the requirements of 812.46 with respect to monitoring investigations;
 - (v) Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);
 - (vi) Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and
 - (vii) Complies with the prohibitions in 812.7 against promotion and other practices.

When the FDA or IRB determines that a study is SR, the IRB may approve the study, but the study cannot begin until an IDE is obtained.

13.7 Humanitarian Use Devices

A Humanitarian Use Device (HUD) is an approved (marketed) medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year [21 CFR 814.3(n)]. Federal law requires that IRBs approve the use of an HUD at a facility. Once approved, the clinical use of the HUD may be considered as any other approved device, with the caution that effectiveness has not been shown in clinical trials.

13.7.1 Definitions

Humanitarian Device Exemption. A Humanitarian Device Exemption (HDE) is a “premarket approval application” submitted to FDA pursuant to Subpart A, 21 CFR Part 814 “seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the [FD&C Act] as authorized by section 520(m)(2) of the [FD&C Act].” HDE approval is based upon, among other criteria, a determination by FDA that the HUD will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

HDE Holder. An HDE Holder is a person who or entity that obtains to approval of an HDE from the FDA.

13.7.2 IRB Review Requirements

A Humanitarian Use Device (HUD) may only be used in a facility after an IRB has approved its use, except in certain emergencies. The HDE holder is responsible for ensuring that a HUD is provided only to facilities having an IRB constituted or rely on an external IRB that acts in accordance with the FDA’s regulations governing IRBs (21 CFR Part 56), including continuing review of use of the device.

When a HUD is used in a clinical investigation (i.e., research involving one or more subjects to determine the safety or effectiveness of the HUD), the full requirements for IRB review and informed consent apply (21 CFR 50 and 56) as well as other applicable regulations. It is essential to differentiate whether the HUD is being studied for the indication(s) in its approved labeling or for different indication(s). When the HUD is being studied for the indication(s) in its approved labeling, the IDE regulations at 21 CFR 812 do not apply. However, when the HUD is being studied for a different indication(s), 21 CFR 812 does apply, including the requirement for a FDA-approved IDE before starting the clinical investigation of a Significant Risk device.

13.7.3 Procedures

The relevant requirements and procedures for investigators and for IRB review described elsewhere in this manual apply to clinical investigations of HUDs. The material within this section applies to diagnostic or treatment uses of HUDs.

The health care provider seeking approval for diagnostic or treatment use of a HUD at University of Virginia is responsible for obtaining IRB approval prior to use of the HUD at the facility and for complying with the applicable regulations, including those for medical device reporting, institutional policies, and the requirements of the IRB.

Health care providers seeking initial IRB approval for diagnostic or treatment use of a HUD for the indication(s) in the HUDs approved labeling should submit the following materials to the IRB

1. A copy of the HDE approval letter with the HDE # from the FDA
2. Cover letter requesting HDE approval. This letter must include the maximum # of subjects planned to use the device and a statement that the device will only be used according to the indications approved under the HDE.
3. [Protocol Information Form for Humanitarian Use Devices](#)
4. A description of the device, such as a device brochure
5. The patient information packet for the HUD
6. The proposed clinical consent process
7. [New Medical Device Request Form](#). This form is completed on line. Once completed, submit with IRB-HSR application. The study team does not need to wait for approval from Clinical Engineering to submit to IRB-HSR.

The IRB will review the proposal at a convened meeting ensuring that appropriate expertise is available either within the membership in attendance or via the use of consultants. The IRB will review the risks to patients that are described in the product labeling and other materials, the proposed procedures to ensure that risks are minimized, and will evaluate whether the risks are reasonable in relation to the potential benefits to patients at the facility. The IRB will evaluate the patient information packet and proposed consent process and will determine if the materials are adequate and appropriate for the patient population.

The IRB may specify limitations on the use of the device, require additional screening and follow up procedures, require interim reports to the IRB, require continuing review more often than annually, or set other conditions or requirements as appropriate to minimize risks to patients and ensure the safe use of the device in the facility.

Once use of the HUD is approved, the health care provider is responsible for submitting any proposed changes to the IRB-approved plan or patient materials and obtaining approval for those changes prior to implementation, unless the change is necessary to avoid or mediate an apparent immediate risk to a patient. Proposed changes may be submitted using the Modification Request Form and should be accompanied by any revised materials or supporting

documentation. The IRB may review these changes using expedited review procedures or refer the changes for review by the convened IRB.

The health care provider is responsible for submitting reports to the FDA, the IRB, and the manufacturer/HDE Holder whenever a HUD may have caused or contributed to a death, and must submit reports to the manufacturer (or to FDA and the IRB if the manufacturer is unknown) whenever a HUD may have caused or contributed to a serious injury (21 CFR 803.30 and 814.126(a)). Serious injury means an injury or illness that (1) is life-threatening, (2) results in permanent impairment of a bodily function or permanent damage to a body structure, or (3) necessitates medical or surgical intervention to preclude permanent impairment of a bodily function or permanent damage to a body structure (21 CFR 803.3). The specific requirements for this reporting are in the Medical Device Reporting (MDR) Regulation, at 21 CFR Part 803. The IRB will review these reports via either expedited or convened review, as appropriate, and will consider whether any changes are needed to the IRB-approved plan or patient materials.

The health care provider is responsible for submitting continuing review materials to the IRB sufficiently in advance of the expiration date to ensure IRB review and re-approval prior to expiration. Materials to be submitted include:

1. The Status Form
2. Any safety reports or summaries provided by the HDE holder that had not previously been submitted
3. The current patient information packet, if applicable
4. The current consent, if applicable
5. Any other new relevant information or materials

The IRB may conduct continuing review using expedited review procedures or review by the convened IRB.

13.7.4 Emergency Uses of HUDs

If a HUD is approved for use in a facility, but an appropriately trained and licensed health care provider wants to use the HUD outside its approved indication(s) in an emergency or determines that there is no alternative device for a patient's condition, the physician should consult with the HDE holder and IRB in advance if possible, obtain informed consent if possible, and ensure that reasonable measures are taken to protect the well-being of the patient such as a schedule and plan for follow up examinations and procedures to monitor the patient, taking into consideration the patient's specific needs and what is known about the risks and benefits of the device. The provider should submit a follow up report to the HDE holder and must comply with medical device reporting requirements. The health care provider must also, within 5 days after the emergency use of the device, provide written notification of the use to the IRB using the [Emergency Use Notification Form](#) which includes the identification of the patient involved via a subject ID# , the date of the use, and the reason for the use.

The IRB may require additional reports, patient protection measures, or other requirement, as appropriate given the specifics of the situation.

13.8 Expanded Access to Investigational Drugs, Biologics, and Devices

Expanded access pathways, also referred to as “compassionate use”, are designed to make investigational medical products available as early in the drug and device evaluation process as possible to patients without therapeutic options, because they have exhausted or are not a good candidate for approved therapies and cannot enter a clinical trial. Expanded access refers to access to investigational medical products outside of a clinical trial, where the intent is treatment, rather than research. Because the investigational products have not yet been approved by FDA as safe and effective, it is important to remember that the product may not be effective and there may be unexpected serious adverse effects and to take appropriate measures to ensure that this is understood by the patient or their representative and to monitor for safety.

13.8.1 Expanded Access to Investigational Drugs and Biologics

The FDA’s expanded access rule for investigational drugs, including biologics classified as drugs, is intended to improve access to investigational drugs, and approved drugs with limited availability under a risk evaluation and mitigation strategy (REMS), for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and may benefit from the investigational diagnostic or therapy.

Under the FDA’s expanded access rule, access to investigational drugs for treatment purposes will be available to:

- Individual patients, including in emergencies [21 CFR 312.310]
- Intermediate-size patient populations [21 CFR 312.315]
- Larger populations under a treatment protocol or treatment IND [21 CFR 312.320]

Expanded access submissions are categorized by FDA as either “Access Protocols”, which involve a protocol amendment to an existing IND, or “Access INDs”, which are managed separately from any existing INDs.

The FDA has also established a rule, “Charging for Investigational Drugs Under an Investigational New Drug Application”, to:

- Provide general criteria for authorizing charging for an investigational drug [21 CFR 312.8(a)]
- Provide criteria for charging for an investigational drug in a clinical trial [21 CFR 312.8(b)]
- Set forth criteria for charging for an investigational drug under the expanded access for treatment use
- Clarify what costs can be recovered

Investigators, when seeking access to drugs under the expanded access provisions, should work closely with the sponsor or manufacturer, the FDA, and the University of Virginia HRPP, to determine the appropriate access mechanism and ensure that proper regulatory procedures are followed.

Unless the conditions that permit an emergency use exemption (see Section 13.9) are satisfied, prospective IRB review and approval is required for all expanded access uses, including clinical patient use. This requires, among other things, that the IRB review the expanded access use at a convened meeting at which a majority of IRB members are present.

When the expanded access use is time-sensitive but does not satisfy the emergency use exemption criteria, and the University of Virginia IRB may not be able to convene within sufficient time to meet the needs of the patient(s), the investigator should consult with the University of Virginia IRB-HSR Director, to determine if use of a central IRB is acceptable.

13.8.2 Expanded Access to Investigational and Unapproved Medical Devices

As with investigational drugs, unapproved medical devices may normally only be used in humans in an approved clinical trial under the supervision of a participating clinical investigator. However, there may be circumstances under which a health care provider may wish to use an unapproved device when a patient is facing life-threatening circumstances or suffering from a serious disease or condition for which no other alternative therapy or diagnostic exists or is a satisfactory option for the patient.

FDA has made the following mechanisms available for these circumstances:

- Emergency Use
- Planned Emergency Research (See Section 11.11.1)
- Compassionate Use (or Single Patient/Small Group Access)
- Treatment Use
- Continued Access

Investigators, when seeking access to investigational or unapproved devices under one of the above provisions, should work closely with the sponsor or manufacturer, the FDA, and the University of Virginia IRB-HSR Director to ensure that proper regulatory procedures are followed.

Unless the conditions that permit an emergency use exemption are satisfied (see Section 13.9), prospective IRB review and approval is required. This requires, among other things, that the IRB review the proposed use at a convened meeting at which a majority of IRB members are present.

When the expanded access use is time-sensitive but does not satisfy the emergency use exemption criteria, and the University of Virginia IRB may not be able to convene within sufficient time to meet the needs of the patient(s), the investigator should consult with the University of Virginia IRB-HSR Director, to determine if use of a central IRB is possible.

13.9 Emergency Use

If an appropriately trained and licensed health care provider in an emergency situation determines that IRB approval for the use of an investigational drug/device at the facility cannot be obtained in time to prevent serious harm or death to a patient, the drug or device may be used without prior IRB approval. The health care provider must, within 5 days after the emergency use of the drug or device, provide written notification of the use to the IRB using the [Emergency Use Notification Form](#) which includes the identification of the patient involved via use of subject ID #, the date of the use, and the reason for the use. Note: DHHS regulations do not permit research activities to be started, even in an emergency, without prior IRB approval. When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject under 45 CFR Part 46. However, nothing in the DHHS regulations at 45 CFR Part 46 is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state or local law.

13.9.1 Emergency Exemption from Prospective IRB Approval

Under FDA regulations [21 CFR 56.104(c)], FDA exempts the emergency use of a test article from the requirement for prospective IRB approval, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article in the facility requires IRB review. However, FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

FDA defines emergency use as the use of a test article in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)]. If all conditions described in 21 CFR 56.102(d) exist then the emergency exemption from prospective IRB approval found at 21 CFR 56.104(c) may be used. The emergency use of a test article, other than a medical device, is a clinical investigation, the patient is a participant, and the FDA may require data from an emergency use to be reported in a marketing application.

For the purposes of 21 CFR 56.102(d), life-threatening includes both life-threatening and severely debilitating.

Unless the provisions for an emergency exception from the informed consent requirement are satisfied (see Section 13.9.2), informed consent must be obtained in accordance with 21 CFR 50 and documented in writing in accordance with 21 CFR 50.27.

The IRB Chair/Vice Chair will review the report to verify that circumstances of the emergency use conformed to FDA regulations. This must not be construed as an approval for the emergency use by the IRB, as an exemption from the requirement for prospective IRB approval has been invoked. The IRB will provide a written statement that the IRB is aware of the use and considers the use to have met the requirements of 21 CFR 56.104(c).

Investigators are reminded that they must comply with all other organizational policies and requirements applicable to the use of the investigational or unapproved article.

13.9.2 Emergency Exception from the Informed Consent Requirement

An exception under FDA regulations at 21 CFR 50.23(a-c) permits the emergency use of an investigational or unapproved test article without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

- a. The subject is confronted by a life-threatening situation necessitating the use of the test article;
- b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
- c. Time is not sufficient to obtain consent from the subject's legally authorized representative; and
- d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the life of the subject.

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent physician determination in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

The IRB must be notified within 5 working days when an emergency exception from informed consent was used by including the information in the [Emergency Use Notification Form](#). The IRB Chair/Vice Chair will review the report to verify that circumstances of the emergency exception conformed to FDA regulations.

13.9.3 Waiver of Informed Consent for Planned Emergency Research

University of Virginia IRB follows FDA regulations, 21 CFR 50.24, and any applicable state requirements which permit waiver of informed consent requirements for emergency research when human subjects in need of emergency medical intervention cannot provide legally effective informed consent and their legally authorized representatives (LARs) are also unable or unavailable to give informed consent on their behalf.

See Section 11.11.1 for additional detail on Planned Emergency Research.

14 Reportable Events

Regulations require an organization to have written procedures for ensuring prompt reporting of changes in research activity; unanticipated problems involving risk to subjects or others; and any instances of serious or continuing non-compliance to the IRB, organizational officials, and applicable federal agencies. In order to comply with this requirement, University of Virginia has procedures to review issues that arise during the conduct of research.

The following section provides definitions and procedures regarding issues that arise during the conduct of research that must be reported to the IRB.

14.1 Definitions

Unanticipated problems involving risk to participants or others. Unanticipated problems involving risks to subjects or others (UPs/UAPs/UPIRTSOs) refer to any incident, experience, outcome, or new information that:

1. Is unexpected
2. Is related or possibly related to participation in the research, and
3. Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, legal or social harm) than was previously known or recognized.

Unexpected. The incident, experience or outcome is not expected (in terms of nature, severity, or frequency) given the research procedures that are described in the study-related documents, such as the IRB-approved research protocol/research plan and informed consent documents; and the characteristics of the subject population being studied.

Related. There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

Adverse Event. For the purposes of these policies and procedures, an adverse event (AE) is any untoward or unfavorable occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

Unanticipated Adverse Device Effect. An Unanticipated Adverse Device Effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subjects [21 CFR 812.3(s)].

Protocol/Research Plan Deviations. A protocol/research plan deviation is defined as a variation from the IRB approved research plan that happens without prior review and approval

of the IRB (e.g., study visit outside protocol/research plan window, blood work drawn outside protocol/research plan window, etc.). Protocol deviations are categorized as major or minor. Depending on the details, protocol/research plan deviations may be determined to be non-compliance (serious, continuing, or otherwise).

Protocol/Research Plan Exceptions. Protocol/research plan exceptions are planned deviations from the protocol/research plan. Exceptions are anticipated and must occur with prior agreement from the sponsor, if applicable, and approval by the IRB. If an exception is implemented without IRB approval, it is a deviation, even when the sponsor has approved.

14.2 Procedures

14.2.1 Reporting

Adverse events in clinical trials must be reported to the sponsor in compliance with FDA regulations and sponsor requirements. **Unless specifically required by the IRB (e.g. first in human clinical trials), the University of Virginia IRB does not accept reports of adverse events and IND Safety Reports that do not meet the definition of an unanticipated problem or an unexpected and serious adverse event involving risks to subjects or others.**

If investigators are uncertain but believe that the event might qualify as an unanticipated problem, a report should be submitted.

Investigators must report the following events or issues to the IRB as soon as possible, but in no event later than 7 days after the investigator first learns of the event.

1. A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
2. A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy.)
3. Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). A summary and analyses supporting the determination should accompany the report.
4. An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects. A discussion of the divergence from the expected specificity or severity should accompany the report.

5. A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). A discussion of the divergence from the expected rate should accompany the report.
6. Changes made to the research without prior IRB approval to eliminate apparent immediate hazards to the subject(s).
7. Adverse events involving direct harm to subjects enrolled by the investigator (i.e., local adverse events), which in the opinion of the investigator or sponsor, may represent an unanticipated problem involving risk to subjects or others.
8. An unanticipated event related to the research that exposes subjects to potential risk but that does not involve direct harm to subjects (e.g. lost laptop).
9. An unanticipated event related to the research that results in actual harm or exposes individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to potential risk.
10. IND Safety Reports from sponsors that meet the criteria for an unanticipated problem involving risk to subjects.
11. Data and Safety Monitoring Reports that indicate that risks are greater than previously known or that indicate that the study requires modification or should be suspended or terminated.
12. New information that indicates an increase to the risks or decrease to potential benefits of the research. Examples include:
 - an interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB
 - a paper is published from another study that shows that the risks or potential benefits of the research may be different than initially presented to the IRB.
13. New information that may impact the willingness of participants to continue in the research.
14. A breach of confidentiality.
15. Incarceration of a participant in a study not approved to enroll prisoners.
16. Complaint of a subject when the complaint involves the health, safety, or rights of the subject or indicates unexpected risks, possible non-compliance, or cannot be resolved by the research team.
17. Protocol/research plan deviations, with the exception of minor deviations. Minor deviations (deviations that do not impact participant safety, compromise the integrity of study data and/or affect the participant's willingness to participate in the research) are kept in the regulatory files by the study team. .

18. Sponsor or lead investigator/coordinating center imposed suspension or termination of some or all research activities.
19. Unanticipated adverse device effects (UADEs). (Note: Regulations require that UADEs be reported to the sponsor and IRB as soon as possible but in no event later than 10 working days after the investigator first learn of the event [21 CFR 812.150(a)(1)]).
20. Any other adverse event or safety finding (e.g. based on animal or epidemiologic data) that indicates subjects or others might be at risk of serious, unanticipated harms that are reasonably related to the research. These would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. An explanation of the conclusion should accompany the report.

14.2.2 Submission of Reports

Investigators or the study team must report possible problems or issues with the research to the IRB Office in writing using the applicable reporting process from the IRB of record. The written report should contain the following:

- a. Detailed information about the event or issue, including relevant dates.
- b. Any corrective and preventative actions, planned or already taken, to ensure that the issue or problem is corrected and will not occur again.
- c. An assessment of whether any subjects or others were placed at risk as a result of the event or suffered any harm (e.g., physical, social, financial, legal or psychological) and any plan to address these consequences.
- d. If a report from a sponsor is the basis for the report of a possible unanticipated problem involving risks to subjects or others, or a sponsor has requested the submission to the IRB, the report should be accompanied by an analysis from the sponsor detailing (1) how the event or problem satisfies the definition of a UAP, (2) proposed study-wide corrective actions or modifications to the research along with a timeline for anticipated completion of the actions, and (3) whether or not the problem has been reported as a UAP to any relevant federal agencies.
- e. If a sponsor or lead investigator or coordinating center suspends or terminates some or all research activities, the report should be accompanied by information from the sponsor detailing (1) why the suspension or termination was enacted, (2) if it was due to a possible UAP (in which case the information in "d" above must be included), (3) any impact on subjects or actions to be taken to protect subjects, (4) any plan to inform subjects of the suspension or termination and other pertinent information, and (5) whether the suspension or termination has been reported to any relevant federal agencies.
- f. Any other relevant information.
- g. Any other information requested by the IRB Office.

Reports will be screened by the IRB staff and immediately forwarded to the IRB Chair, or designee if the IRB staff believes that immediate intervention may be required to protect participants or others from serious harm.

Upon receipt of a report or complaint of from someone other than the investigator or study staff on behalf of the investigator, the IRB

Director or designee will notify the investigator when appropriate.

14.2.3 IRB Procedures for Handling Reportable Events

1. Upon receipt of the reportable event from an investigator, the IRB staff checks the information for completeness. If any of the information is incomplete or has been answered unsatisfactorily, the IRB staff will contact the investigator or the designated contact person to obtain additional information. Corrections are documented in the IRB file, indicating the date, the person spoken with, and the IRB staff making the correction.
2. The IRB Chair and/or other experienced member(s) designated by the IRB Chair receives and reviews the report. The IRB Chair (or designee) will make the initial determination as to whether the event is to be regarded as an unanticipated problem and/or non-compliance (See Section 15 for procedures for unanticipated problems, and Section 16 for serious or continuing non-compliance).
3. Based on the information received from the investigator, the IRB Chair or designee may suspend research to ensure protection of the rights and welfare of participants. Suspension directives made by the IRB Chair or designee must be reported to a meeting of the convened IRB and must follow notification procedures for IRB suspensions.
4. The IRB or the IRB Chair (or designee) has authority to require submission of more detailed contextual information by the investigator, the sponsor, the study coordinating center, or DSMB/DMC about any event occurring in a research study as a condition of the continuation of the IRB's approval of the research.
5. If the IRB Chair or designee determines that the problem does not possibly meet the definition of an unanticipated problem or serious or continuing non-compliance, the reviewer will consider whether any corrective or preventative actions are sufficient and whether modifications to the research plan, consent, or corrective action plan may be necessary, and refer the matter to the convened IRB for review if appropriate. The results of the review will be recorded in the study record and communicated to the investigator.
6. If the reviewer determines that the event may be an unanticipated problem, the report will be reviewed at a convened IRB meeting and must follow notification procedures for UPs.

15 Unanticipated Problems Involving Risks to Subjects or Others

University of Virginia complies with DHHS and FDA regulations which require organizations to have written policies on reporting unanticipated problems involving risks to subjects or others (UP/UAP/UPRIRTSO) to the IRB, organizational officials and relevant federal agencies and departments.

The following procedures describe how UAPs are handled in research under the auspices of University of Virginia. Unless specifically required by the IRB, the University of Virginia IRB does not accept reports of adverse events that do not meet the definition of an UAP.

15.1 IRB Review

After a determination of a possible unanticipated problem involving risk to subjects or others (UAP), the report will be placed on the agenda for the next convened IRB meeting and a primary reviewer will be assigned.

The primary reviewer will be given the study file, the currently approved consent document, previous reports of UAPs, the investigator's brochure (if one exists), the event report, and recommendations from the IRB Chair or designee, when appropriate. All IRB members will receive the event report and have full access to all materials upon request.

After review of the study and event report, the full IRB will make findings and recommendations based on the following considerations:

- Whether the reported event is a UAP according to the definition in this policy.
 - What action in response to the report is appropriate.
 - Whether suspension or termination of approval is warranted.
1. If the IRB finds that the event is not a UAP, according to the definition in the policy, the IRB may recommend any of the following actions:
 - a. No action
 - b. Requiring modifications to the protocol/research plan
 - c. Revising the continuing review timetable
 - d. Modifying the consent process
 - e. Modifying the consent document
 - f. Providing additional information to current participants (e.g., whenever the information may relate to the subject's willingness to continue participation)
 - g. Providing additional information to past subjects
 - h. Requiring additional training of the investigator and/or study staff
 - i. Other actions as appropriate given the specific circumstances

2. If the IRB finds that the event is a UAP, according to the definition in the policy, the IRB may recommend any of the following actions:
 - a. Requiring modifications to the protocol/research plan
 - b. Revising the continuing review timetable
 - c. Modifying the consent process
 - d. Modifying the consent document
 - e. Providing additional information to current participants (e.g., whenever the information may relate to the subject's willingness to continue participation)
 - f. Providing additional information to past participants
 - g. Requiring additional training of the investigator and/or study staff
 - h. Reconsidering approval
 - i. Requiring that current subjects re-consent to participation
 - j. Monitoring the research
 - k. Monitoring consent
 - l. Referral to other organizational entities (e.g., legal counsel, risk management, Institutional Official)
 - m. Suspending the research approval
 - n. Terminating the research approval
 - o. Other actions as appropriate given the specific circumstances
3. If a report suggests that participant safety is at risk, the IRB may immediately suspend or terminate the research. Any suspension or termination of research by the IRB must be promptly reported to the IO and relevant federal regulatory agencies through the IO. This should be done in writing.
4. If, after reviewing a report, the IRB finds that the event is a UAP or that suspension or termination of approval is warranted, the IRB will:
 - a. Notify the investigator in writing of its findings, with copies to the Chair of the investigator's department and/or research unit, other affected units and the investigator's supervisor, and
 - b. Report its findings and recommendations to the Vice President for Research for further reporting to the appropriate federal officials (see Section 18).

16 Non-compliance

As part of its commitment to protecting the rights and welfare of human subjects in research, University of Virginia reviews all reports and allegations of non-compliance and takes any necessary action to ensure the ethical conduct of research.

All Investigators and other study personnel involved in human subject research are required to comply with all laws and regulations governing their research activities, as well as with requirements and determinations of the IRB.

The following procedures describe how complaints and allegations of non-compliance are handled by the IRB.

16.1 Definitions

Non-compliance. Non-compliance is defined as failure to adhere to federal, state, or local regulations governing human subject research, organizational policies related to human subject research, or the requirements or determinations of the IRB. Non-compliance may be minor or sporadic or it may be serious or continuing.

Serious non-compliance. Serious non-compliance is defined as non-compliance that, in the judgment of the convened IRB, creates an increase in risks to subjects, adversely affects the rights, welfare or safety of subjects, or adversely affects the scientific integrity of the study. Willful violation of regulations and/or policies may also constitute serious non-compliance.

Continuing non-compliance. Continuing non-compliance is defined as a pattern of non-compliance that, in the judgment of the convened IRB, suggests a likelihood that instances of non-compliance will continue unless the IRB or organization intervenes.

Allegation of Non-Compliance. Allegation of Non-Compliance is defined as an unproved assertion of non-compliance.

Finding of Non-Compliance. Finding of Non-Compliance is defined as an allegation of non-compliance that is proven true or a report of non-compliance that is clearly true. (For example, a finding on an audit of an unsigned consent document, or an admission of an investigator of that the protocol/research plan was willfully not followed would represent reports of non-compliance that would require no further action to determine their truth and would therefore represent findings of non-compliance.) Once a finding of non-compliance is proven, it must be categorized as minor non-compliance, serious, sporadic or continuing.

16.2 Reporting

Investigators and their study staff are required to report instances of possible non-compliance. The investigator is responsible for reporting any possible non-compliance by study personnel to the IRB. However, any individual or employee may report observed or apparent instances of non-compliance to the University of Virginia IRB. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality and cooperating with any IRB and/or organizational review of these reports.

If an individual, whether investigator, study staff or other, is uncertain whether there is cause to report non-compliance, he or she may contact the IRB Staff or Chair directly to discuss the situation informally.

Reports of non-compliance must be submitted to the IRB Office within 7 working days of discovery of this non-compliance. The report must include a complete description of the non-compliance including any personnel involved.

Complainants may choose to remain anonymous.

16.3 Review of Allegations of Non-compliance

All allegations of non-compliance will be reviewed by the IRB Chair or designee, who will review the report or allegation and may request additional information or an audit of the research in question.

When the Chair or designee determines that non-compliance did not occur because the incident was within the limits of an approved protocol/research plan for the research involved, the determination is reported in writing to the investigator and, if applicable, the reporting party. The determination letter will be copied to the Institutional Official in cases where the Institutional Official and any other parties had been notified of the allegation at the outset.

If in the judgment of the IRB Chair or designee, the report or allegation does represent non-compliance, the non-compliance will be processed according to Section 16.4 (Review of Findings of Non-compliance).

If in the judgment of the IRB Chair or designee, any allegation or findings of non-compliance warrants suspension of the research before completion of any review or investigation to ensure protection of the rights and welfare of participants, the IRB Chair may suspend the research as described in Section 8 with subsequent review by the IRB.

The Chair or designee may determine that additional expertise or assistance is required to make these determinations and may request assistance from the HRPP Director, IRB personnel or from an *ad hoc* committee to assist with the review and fact gathering process. When an *ad hoc* committee assists in the review process, the Chair or designee is responsible for assuring that minutes of the meeting are generated and kept to help support any determinations or findings made by the *ad hoc* committee.

16.4 Review of Findings of Non-compliance

16.4.1 Non-compliance that is not serious or continuing:

When the Chair or designee determines that the non-compliance occurred, but the non-compliance does not meet definition of serious or continuing non-compliance, the determination is reported in writing to the investigator and, if applicable, the reporting party. The Chair will review any corrective and preventative actions taken or proposed by the investigator and determine if the actions are sufficient or if additional actions may be

necessary. In the event that additional actions may be warranted, the matter will be referred to the convened IRB for review.

16.4.2 Serious or Continuing Non-compliance

When the Chair or designee determines that non-compliance has occurred and that the non-compliance may meet the definition of serious or continuing non-compliance, the report of non-compliance is referred for review by the IRB at the next available convened meeting. However, the Chair or designee may use discretion and call an emergency IRB meeting should the circumstances warrant an urgent meeting.

All initial findings of potential serious or continuing non-compliance referred to the IRB will be reviewed at a convened meeting.

At this stage, the IRB may:

1. Find that there is no issue of non-compliance
2. Find that there is non-compliance that is neither serious nor continuing and that an adequate corrective and/or preventive action plan is in place
3. Find that there is serious or continuing non-compliance and modify or require a corrective and/or preventive action plan
4. Find that additional information is required to make a final determination. In this instance, the committee will request additional information, and indicate whether such information will be reviewed by the full committee or a subcommittee thereof; if the latter, a report will be written by the subcommittee for review by the full committee for final determination.

16.4.3 Final Review

The IRB will make a final determination as to whether the non-compliance is serious or continuing. Upon a finding of serious or continuing non-compliance, the IRB's possible actions could include, but are not limited to:

1. Request a corrective and/or preventive action plan from the investigator
2. Verification that subject selection is appropriate
3. Observation of informed consent
4. Require an increase in data and safety monitoring of the research activity
5. Request a directed audit of areas of concern
6. Request a status report after each participant receives intervention
7. Modify the continuing review cycle
8. Require additional investigator and staff education

9. Notify current subjects (e.g., if the information about the non-compliance might affect their willingness to continue participation)
10. Require modification of the protocol/research plan.
11. Require modification of the information disclosed during the consent process.
12. Require current subjects to re-consent to participation.
13. Suspend the study (See below); or
14. Terminate the study (See below)

In cases where the IRB determines that the event of non-compliance also meets the definition of unanticipated problem involving risks to subjects or others, it will be handled according to Section 15.

The investigator is informed of the IRB determination and the basis for the determination in writing. If the IRB determines that the non-compliance was serious or continuing, the results of the final review will be reported as described below in Section 18.

17 Complaints

The [IRB Director] will promptly handle (or delegate staff to handle), and, if necessary, investigate all complaints, concerns, and appeals received by the IRB Office. This includes complaints, concerns, and appeals from investigators, research participants and others.

All complaints, written or oral (including telephone complaints), and regardless of point of origin, are recorded in writing and forwarded to the IRB Director.

Upon receipt of the complaint, the IRB Director will make a preliminary assessment whether the complaint warrants immediate suspension of the research project. If a suspension is warranted, the procedures in Section 8 will be followed.

If the complaint may meet the definition of non-compliance, it will be considered an allegation of non-compliance according to Section 16.

If the complaint may meet the definition of an unanticipated problem involving risk to subjects or others, it will be handled according to Section 15.

If the complaint is actually a query from a subject regarding study procedures, payments not received, etc., it will be forwarded to the investigator/study team for handling. The investigator/study team will be required to inform the IRB when the matter is closed (and the subject is satisfied with the answer).

Within 3 business days of receipt of the complaint, the IRB Director will generate a letter to acknowledge that the complaint has been received and is being investigated, if the person making the complaint provided contact information.

18 Reporting to Regulatory Agencies and Organizational Officials

Federal regulations require prompt reporting to appropriate organizational officials and, as applicable, the federal department or agency head or the FDA, of (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing non-compliance with this policy or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval. University of Virginia IRB complies with this requirement as follows.

18.1 Procedures

- 1) IRB staff will initiate these procedures as soon as the IRB takes any of the following actions:
 - a. Determines that an event may be considered an unanticipated problem involving risks to participants or others
 - b. Determines that non-compliance was serious or continuing
 - c. Suspends or terminates approval of research
- 2) The IRB Director or designee is responsible for preparing reports or letters which includes the following information: (
 - a. The nature of the event (Unanticipated problem involving risks to participants or others, serious or continuing non-compliance, suspension or termination of IRB approval of research)
 - b. Name of the institution conducting the research
 - c. Title of the research project and/or grant proposal in which the problem occurred
 - d. Name of the investigator on the project
 - e. Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement)
 - f. A detailed description of the problem including the findings of the organization and the reasons for the IRB's decision
 - g. Actions the institution is taking or plans to take to address the problem (e.g., revise the protocol/research plan, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.)
 - h. Plans, if any, to send a follow-up or final report by the earlier of
 1. A specific date
 2. When an investigation has been completed or a corrective action plan has been implemented
- 3) The IRB Chair/vice chair will review the letter, make modification as needed and sign.

- 4) The IRB Director or designee sends a copy of the report to:
- a. The IRB by including the letter in the next agenda packet as an information item
 - b. The Institutional Official
 - c. The following federal agencies:
 - OHRP, if the study is subject to DHHS regulations or subject to a DHHS FWA.
 - FDA, if the study is subject to FDA regulations.
 - If the study is conducted or funded by any Federal Agency other than DHHS that is subject to “The Common Rule”, the report is sent to OHRP or the head of the federal agency as required by the agency.
 - Reporting to a regulatory agency is not required if the event occurred at a site that was not subject to the direct oversight of the organization, and the agency has been notified of the event by the investigator, sponsor, another organization, or other mechanisms.
 - d. Investigator
 - e. Sponsor, if the study is sponsored
 - f. [Chairman or supervisor of the investigator]
 - g. [The Privacy Officer of a covered entity, if the event involved unauthorized use, loss, or disclosure of individually-identifiable patient information from a covered entity]
 - h. [The Information Security Officer of an organization, if the event involved violations of information security requirements of that organization]
 - i. [Office of Risk Management, if appropriate]
 - j. Others as deemed appropriate by the Institutional Official

The IRB Director ensures that all steps of this policy are completed within 30 working days of the determination. For more serious actions, the Director will expedite reporting.

19 Investigator Responsibilities

Investigators are ultimately responsible for the conduct of research. Investigators may delegate tasks to appropriately trained and qualified members of their research team. However, investigators must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibilities.

19.1 Investigators

The research team is made up of ‘investigators’, differentiated as follows, along with their responsibilities in the conduct of research involving human participants.

Principal Investigators (PI)

At the University of Virginia only faculty or staff members with University of Virginia appointments may serve as the PI or as the faculty sponsor on a research project involving human subjects. The only exception is that students are allowed to serve as the PI on non-medical research if sponsored by a faculty advisor.

The IRB recognizes one PI for each study. The PI has ultimate responsibility for the research activities.

Studies that require expertise or skills beyond those held by the PI must either be modified or have expertise and skills supplemented by the inclusion of one or more additional qualified sub-investigators.

Sub-Investigators

A sub-investigator is any individual other than the PI who is involved in the conduct of a research study. Such involvement could include:

- Obtaining information about living individuals by intervening or interacting with them for research purposes;
- Obtaining identifiable private information about living individuals for research purposes;
- Obtaining the voluntary informed consent of individuals to be subjects in research; and
- Studying, interpreting, or analyzing identifiable private information or data for research purposes.

19.2 Responsibilities

In order to satisfy the requirements of this policy, investigators who conduct research involving human subjects must:

1. Develop and conduct research that is in accordance with the ethical principles in the Belmont Report;
2. Develop a research plan that is scientifically sound and minimizes risk to the subjects;

3. Incorporate into the research plan a plan to ensure the just, fair, and equitable recruitment and selection of subjects;
4. When some or all of the subjects are likely to be vulnerable to coercion or undue influence(e.g., children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons), include additional safeguards in the study to protect the rights and welfare of these subjects;
5. Ensure that the research plan includes adequate provisions for the monitoring of subjects and data to ensure the safety of subjects;
6. Ensure that there are adequate provisions to protect the privacy interests of subjects;
7. Ensure that there are adequate provisions to protect data confidentiality and interests of subjects, including an information security plan that considers the collection, storage, maintenance, analysis, and transmission of data and other identifiable information;
8. Have sufficient resources necessary to protect human subjects, including:
 - a. Access to a population that would allow recruitment of the required number of subjects.
 - b. Sufficient time to conduct and complete the research.
 - c. Adequate numbers of qualified staff.
 - d. Adequate facilities.
 - e. Necessary equipment.
 - f. A plan to ensure proper supervision of the research including a plan for periods of absence or decreased availability.
 - g. Availability of medical, psychological, or other support that subjects might require during or as a consequence of their participation in the research.
9. Assure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise qualified to perform such under the laws of Virginia and the policies of University of Virginia;
10. Assure that all study personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based;
11. Assure that all persons assisting with the research are adequately trained and informed about the protocol/research plan and their specific duties and functions.
12. Promptly report any changes in, addition to, or departure of investigators or research staff to the IRB for evaluation and approval (note that investigators and staff may not begin work on the research until IRB-approved);
13. Protect the rights, safety, and welfare of participants;

14. Ensure that when private health information is used, legally effective HIPAA authorization is obtained for each subject unless the Privacy Board or IRB has approved a waiver of the requirement;
15. Ensure that the language in the consent form is consistent with that in the protocol/research plan and, when applicable, in the HIPAA authorization;
16. Obtain and document informed consent and ensure that no human subject is involved in the research prior to obtaining consent or consent/permission from their legally authorized representative, unless a waiver of the requirement has been approved by the IRB;
17. Have a procedure to receive questions, complaints, or requests for additional information from subjects and respond appropriately;
18. Ensure that all information provided to the IRB is accurate and complete so that the IRB may fulfill its responsibilities to review the research and make the required determinations;
19. Ensure that all research involving human subjects receives IRB review and approval in writing or a determination of exemption before research begins;
20. Ensure that all research involving human subjects is reviewed by other experts and organizational components and committees as applicable to the research;
21. Comply with all IRB decisions, conditions, and requirements;
22. Ensure that studies receive timely continuing IRB review and approval;
23. Report unanticipated problems, deviations, complaints, non-compliance, suspensions, terminations, and any other reportable events to the IRB;
24. Notify the IRB if information becomes available that suggests a change to the potential risks or benefits of the research
25. Obtain IRB review and approval before changes are made to the research unless a change is necessary eliminate apparent immediate hazards to the subject(s);
26. When following ICH-GCP (E6) guidelines :
 - a. During and following a subject's participation in a clinical trial, the researcher ensures that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the clinical trial.
 - b. The researcher follows the clinical trial's randomization procedures, if any, and ensures that the code is broken only in accordance with the protocol. If the clinical trial is blinded, the researcher promptly documents and explains to the Sponsor any premature unblinding.
 - c. A qualified physician (or dentist, when appropriate) who is a researcher for the clinical trial, is responsible for all clinical trial-related medical (or dental) decisions.

- d. Researchers inform subjects in an active study when medical care is needed for other illnesses of which the researchers become aware.
 - e. Although a subject is not obliged to give his or her reasons for withdrawing prematurely from a clinical trial, the researcher makes a reasonable effort to ascertain the reason, while fully respecting the subject's rights.
27. Seek IRB assistance when in doubt about whether proposed research requires IRB review;
28. Retain records for the time period and in the manner required by applicable regulations, contractual agreements, and organizational policies.
29. The researcher reports all serious adverse events (SAEs) to the sponsor except for those SAEs that the protocol or other document (e.g., investigator's brochure) identifies as not needing immediate reporting. The researcher follows regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authority and the IRB.
30. The researcher reports adverse events or laboratory abnormalities identified in the protocol as critical to safety evaluations to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
31. For reported deaths, the researcher supplies the sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).
32. The researcher provides written reports to the sponsor, the IRB, and, where applicable, the organization on any changes significantly affecting the conduct of the clinical trial or increasing the risk to subjects.
33. If the researcher terminates or suspends a clinical trial without prior agreement of the sponsor, the researcher informs the organization, sponsor, and the IRB.
34. If the IRB terminates or suspends approval of the clinical trial, the researcher promptly notifies the sponsor.
35. Upon completion of the clinical trial, the researcher informs the organization; the IRB with a summary of the trial's outcome; and the regulatory authority with any reports required.

Additional investigator responsibilities, including specific responsibilities for investigators engaged in FDA-regulated research are described elsewhere in this document.

19.3 Investigator Records

Under these policies investigators must maintain, at a minimum but not limited to, the following research records under these policies. In addition, investigators must also comply with all record-keeping sponsor requirements.

19.3.1 Study Records

- Individual subject records
- Recruitment materials
- Documentation of consent process (who, what, when and how)
- Signed consent forms
- Unanticipated Problem & Reportable Event Reports
- Subject complaint reports
- Results of all procedures conducted on the subject, including final visit (if no final visit, reason why: e.g., removal from study, withdrawal from study, death)

19.3.2 Regulatory Records

- Most recent IRB-approved protocol/research plan
- Previous versions of protocol/research plan
- All correspondence (i.e., approvals, reporting forms and responses, etc.) to and from the IRB
- All correspondence with the sponsor and others regarding the study
- Continuing review progress reports
- Modification Requests
- Investigational product accountability records, when applicable

19.3.3 Record Retention

Investigator records must be retained in accordance with regulatory, organizational and sponsor or grantor requirements, but no less than three (3) years following the completion of the research. All records must be maintained securely with limited access. Disposal of investigator records must be done in such a manner that no identifying information can be linked to research data. *(Note that organizational policies on ownership of research data also must be followed.)*

19.4 Investigator Concerns

Investigators who have concerns or suggestions regarding University of Virginia 's HRPP or IRB(s) should convey them to the Institutional Official or other responsible parties (e.g., supervisor, college dean, departmental Chair), when appropriate. The Institutional Official will consider the issue, and when deemed necessary, seek additional information and convene the parties involved to form a response for the investigator or make necessary procedural or policy

modifications, as warranted. In addition, the Chair of the IRB or the IRB Director will be available to address investigators' questions, concerns and suggestions.

In addition to these SOPs, which are made available on the University of Virginia website for investigators, investigators are also made aware of the process for expressing their concerns via a link on the University of Virginia website for concerns or complaints.

20 Sponsored Research

It is University of Virginia policy that any sponsored research conducted under the auspices of the Organization is conducted in accordance with federal guidelines and ethical standards.

The following describe the procedures required to ensure that all sponsored research meets this requirement.

20.1 Definitions

Sponsor. Sponsor means the company, institution, individual donor, or organization responsible for the initiation, management or financing of a research study.

Sponsored research. Sponsored research means research funded by external entities (public, industry, or private) through a grant or contract that involves a specified statement of work (e.g., the research proposal), including clinical trials involving investigational drugs, devices or biologics.

20.2 Responsibility

Sponsor grants, contracts, and other written agreements will be reviewed for the following by the Office of Sponsored Programs, with consultation with the IRB, as necessary:

1. All industry contracts have a written agreement with the Sponsor that addresses medical care for research participants with a research-related injury, when appropriate, or lack of research-related injury has been reviewed and approved by the appropriate representative of the Dean's Office in the school.
2. Where appropriate, in studies where Sponsors conduct research site monitoring visits or conduct monitoring activities remotely, the University of Virginia requests that the sponsor contracts have a written agreement with the Sponsor that the Sponsor promptly reports to the University of Virginia findings that could affect the safety of participants or influence the conduct of the study, or lack of such provision has been reviewed and approved by the appropriate Dean's representative. Experience suggests prompt notice to be not longer than 30 days from a finding, but it is acknowledged the default contract language does not expressly bind the Sponsor to a 30-day window. Sponsors who do not accept the default safety notification clause will be counselled on the rationale behind prompt notice and offered alternatives.
3. Where appropriate, when the Sponsor has the responsibility to conduct data and safety monitoring, the sponsor contracts have a written agreement with the Sponsor that addresses provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to the University of Virginia, or lack of such provision has been reviewed and approved by the appropriate Dean's representative.
4. Sponsor contracts have a written agreement with the Sponsor about plans for disseminating findings from the research and the roles that investigators and Sponsors will play in the publication or disclosure of results.

5. When participant safety could be directly affected by study results after the study has ended, where appropriate, the sponsor contracts have a written agreement with the Sponsor that the investigator or University of Virginia will be notified of the results in order to consider informing participant, or lack of such provision has been reviewed and approved by the appropriate Dean's representative.
6. Payment in exchange for referrals of prospective participants from investigators (physicians) ("finder's fees") is not permitted. Similarly payments designed to accelerate recruitment that are tied to the rate or timing of enrollment ("bonus payments") are also not permitted.

21 Conflict of Interest in Research

It is University of Virginia policy to preserve public trust in the integrity and quality of research by reducing actual or perceived conflict of interest in the conduct of research.

Conflicts of interest ('COI') in research can be broadly described as any interest that competes with an organization's or individual's obligation to protect the rights and welfare of research subjects, the integrity of a research study, or the credibility of the research program. Conflicts of interest can be financial or non-financial.

In the environment of research, openness and honesty are indicators of integrity and responsibility, characteristics that promote quality research and strengthen the research process. Therefore, conflicts of interest should be eliminated when possible and effectively managed and disclosed when they cannot be eliminated.

21.1 Researcher Conflicts of Interest

Pursuant to the Conflict of Interest policy "[RES 005: *Financial Conflicts of Interest for Research Investigators*]", University of Virginia maintains a Conflict of Interest Committee ("COI Committee"). University of Virginia IRB will collaborate with the COI Committee to ensure that COI of researchers and research staff ('researchers') are identified and managed before the IRB completes its review of any research application.

21.1.1 Procedures

21.1.1.1 Disclosure of Researcher COI

For IRB purposes, researcher conflict review occurs at the time of new study submission, continuing review, with the addition of a new researcher, and whenever a researcher updates their University of Virginia COI disclosure indicating a new or changed interest. IRB staff notify the COI Chair whenever a submission requiring conflict review is received. The COI Chair reviews the researchers' disclosures and either notifies the IRB staff that no researcher COI was identified or that one or more researchers has an interest that requires evaluation by the COI Committee. In the event a conflict that requires disclosure or management is identified, the COI Chair will provide to the IRB in writing with a summary of conflict and the conflict management plan ('CMP') approved by the COI Committee. If the COI Committee has not completed its review, the IRB will defer the research study review or prohibit participation by the researcher with a potential COI until the COI Committee review process is completed and the results are made available to the IRB.

21.1.1.2 Evaluation of COI

The IRB will review COI and CMP to determine:

- Whether the COI affects the rights or welfare of research subjects,

- Whether the COI might adversely affect the integrity or credibility of the research or the research program, and
- Whether the CMP effectively protects research subjects and the integrity and credibility of the research and the research program

The IRB will consider:

- How the research is supported or financed,
- The nature and extent of the conflict,
- The role and responsibilities of the conflicted individual in the design, conduct, and reporting of the research, and
- The ability of the conflicted individual to influence the outcome of the research

21.1.1.3 Management of COI

The IRB has final authority to determine whether the research, the COI, and the CMP, if any, allow the research to be approved. With regard to the CMP issued by the COI Committee, the IRB shall either affirm or request changes to strengthen it. The IRB can require additional measures to manage a COI so that the research may be approved. However, the IRB cannot weaken a CMP approved by the COI Committee.

For example, in addition to the CMP, the IRB may require:

1. Disclosure of the COI to subjects through the consent process
2. Modification of the research plan or safety monitoring plan
3. Monitoring of research by a third party
4. Disqualification of the conflicted party from participation in all or a portion of the research
5. Appointment of a non-conflicted PI
6. Divestiture of significant financial interests
7. Severance of relationships that create actual or potential conflicts.

In the event the conflict cannot be effectively managed, the IRB may disapprove the research.

21.2 IRB Member Conflict of Interest

No IRB member or alternate (note: “IRB member” in this section includes IRB staff and consultants) may participate in the review of any research project in which the member has a conflict of interest (COI), except to provide information as requested. It is the responsibility of each IRB member to disclose any COI related to a study submitted for review and recuse him/herself from the deliberations and vote by leaving the room.

All members and alternate members of the IRB complete an “IRB Member Conflict of Interest Statement” when first appointed and annually thereafter.

IRB members, alternates, or consultants may be considered to have a conflicting interest requiring recusal when they, or an immediate member of their family, have any of the following:

1. Involvement in the design, conduct, and reporting of the research,
2. Significant financial interests (See *[IRB Member Conflict of Interest Statement]* for a definition of significant financial interests) related to the research being reviewed,
3. Any other situation where an IRB member believes that another interest conflicts with his or her ability to deliberate objectively on a study.

The IRB Chair will ask IRB members at the beginning of each convened meeting if any members have a COI regarding any of the items to be reviewed and reminds members that they must recuse themselves by leaving the room during the discussion and vote of the specific research study. If a conflicted member is participating by conference call, videoconference or web meeting, the member’s participation (connection) is terminated for discussion and voting.

IRB members with a conflicting interest are excluded from being counted towards quorum. Recusals of members with COIs are recorded in the minutes.

21.3 Institutional Conflict of Interest

The Institutional Conflict of Interest (“ICOI”) policy (“University of Virginia Institutional Conflict of Interest Policy”) outlines University-wide requirements regarding ICOI. It covers the entire University and applies to both the interests of the Institution itself and the interests of senior university officials. It is a comprehensive policy covering all institutional activities including, but not limited to, research, education, patient care, and professional and business practices. Pursuant to the ICOI policy, the President will appoint an ICOI official who will have responsibility for the implementation of this policy. The University will maintain an Institutional COI Committee, which may be the same as the Research COI Committee. The ICOI official will oversee the monitoring of the financial interests of the Institution and senior university officials and will work with the ICOI Committee to evaluate and manage ICOI.

21.4 Recruitment Incentives

Payment arrangements among sponsors, organizations, investigators, and those referring research participants present a conflict of interest and may place participants at risk of coercion or undue influence or cause inequitable selection. Payment in exchange for referrals of prospective participants (“finder’s fees”) is not permitted. Similarly payments designed to accelerate recruitment that is tied to the rate or timing of enrollment (“bonus payments”) are also not permitted.

22 Participant Outreach

University of Virginia is committed to ensuring that educational opportunities are offered to research participants, prospective research participants, and community members which will enhance their understanding of research involving human participants at University of Virginia and provide them the opportunity to provide input and express concerns.

The following procedures describe how University of Virginia fulfills that responsibility.

22.1 Responsibility

It is the responsibility of the IRB Directors to implement the procedures outlined below.

22.2 Outreach Resources and Educational Materials

1. The HRPP office dedicates a section of the website to research participants entitled “For Research Subjects.” This website includes resources, such as Frequently Asked Questions (FAQs), University of Virginia designed brochures (Volunteering in Research), and a listing of relevant research-related links.
2. The “For Research Subjects” includes information regarding how to contact University of Virginia with any questions or concerns about specific research projects or research in general.
3. The “For Research Subjects” includes a “Contact Us” link that allows members of the community to ask questions, express concerns, or provide feedback. Provision of contact information by the person is optional.
4. University of Virginia periodically provides presentations related to research to community organizations.
5. University of Virginia holds an annual “Research Day” to which members of the public are invited.

22.3 Evaluation

On an annual basis, University of Virginia evaluates its outreach activities and makes changes when appropriate. In order to formally evaluate its outreach activities, the IRB Directors will review:

1. The specific community outreach activities being used
2. Whether or not these community outreach activities have an evaluative component (e.g., evaluation instrument distributed to participants), and if so whether the feedback was positive, negative, or neutral and if any suggestions were made that could be used to enhance future activities.
3. The number of times the “For Research Subjects” is visited
4. Feedback provided via the “Contact Us” mechanism on the “For Research Subjects”

5. Feedback provided from other sources (unaffiliated IRB members, investigators, research staff, students, etc.)

The results of the review will be used to establish both the adequacy of current outreach activities and any additional resources that may be needed to meet the needs of the research community regarding participant outreach.

23 Health Insurance Portability and Accountability Act (HIPAA)

The *Health Insurance Portability and Accountability Act of 1996* (HIPAA) required the creation of a Privacy Rule for identifiable health information. While the primary impact of the Privacy Rule is on the routine provision of and billing for health care, the Rule also affects the conduct and oversight of research.

The Privacy Rule defines individually identifiable health information transmitted or maintained by a covered entity in any form (electronic, written or oral) as “protected health information” (PHI) and establishes the conditions under which investigators may access and use this information in the conduct of research.

Except as otherwise permitted, the Privacy Rule requires that a research subject “authorize” the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject’s consent to participate in research, which is required under the Common Rule and FDA regulations.

Under the Privacy Rule, a HIPAA Authorization may be combined with the consent document for research. When the consent document is combined with an Authorization as it is at University of Virginia, 45 CFR part 46 and 21 CFR part 56 require IRB review of the combined document.

At University of Virginia, for exempt projects and other categories of research not subject to IRB or Privacy Board oversight, the HRPP Office is designated to act upon requests for waivers and alterations of the Authorization requirement for research purposes.

23.1 Definitions (per HIPAA Privacy Rule Booklet for Research)

Access. Access is the mechanism of obtaining or using information electronically, on paper, or other medium for the purpose of performing an official function.

Accounting of Disclosures. Information that describes a covered entity’s disclosures of PHI other than for treatment, payment, and health care operations; disclosures made with Authorization; and certain other limited disclosures. For those categories of disclosures that need to be in the accounting, the accounting must include disclosures that have occurred during the 6 years (or a shorter time period at the request of the individual) prior to the date of the request for an accounting. However, PHI disclosures made before the compliance date for a covered entity are not part of the accounting requirement.

Authorization. An individual’s written permission to allow a covered entity to use or disclose specified PHI for a particular purpose. Except as otherwise permitted by the Privacy Rule, a covered entity may not use or disclose PHI for research purposes without a valid Authorization.

Covered entity. A health plan, a health care clearinghouse, or a health care provider who transmits health information in electronic form in connection with a transaction for which DHHS has adopted a standard.

Data Use Agreement. An agreement into which the covered entity enters with the intended recipient of a limited data set that establishes the ways in which the information in the limited data set may be used and how it will be protected.

Designated Record Set. A group of records maintained by or for a covered entity that includes (1) medical and billing records about individuals maintained by or for a covered health care provider; (2) enrollment, payment, claims adjudication, and case or medical management record systems maintained by or for a health plan; or (3) used, in whole or in part, by or for the covered entity to make decisions about individuals. A record is any item, collection, or grouping of information that includes PHI and is maintained, collected, used, or disseminated by or for a covered entity.

Disclosure. The release, transfer, access to, or divulging of information in any other manner outside the entity holding the information.

Health Information. Health Information means any information, whether oral or recorded in any form or medium, that (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.

Individually Identifiable Health Information. Information that is a subset of health information, including demographic information collected from an individual, and (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; and (a) that identifies the individual; or (b) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

Limited Data Set. Refers to PHI that excludes 16 categories of direct identifiers and may be used or disclosed, for purposes of research, public health, or health care operations, without obtaining either an individual's Authorization or a waiver or an alteration of Authorization for its use and disclosure, with a data use agreement.

Minimum Necessary. The standard that uses the least information reasonably necessary to accomplish the intended purpose of the use, disclosure, or request. Unless an exception applies, this standard applies to a covered entity when using or disclosing PHI or when requesting PHI from another covered entity. A covered entity that is using or disclosing PHI for research without Authorization must make reasonable efforts to limit PHI to the minimum necessary. A covered entity may rely, if reasonable under the circumstances, on documentation

of IRB or Privacy Board approval or other appropriate representations and documentation under section 164.512(i) as establishing that the request for protected health information for the research meets the minimum necessary requirements.

Privacy Board. A board that is established to review and approve requests for waivers or alterations of Authorization in connection with a use or disclosure of PHI as an alternative to obtaining such waivers or alterations from an IRB. A Privacy Board consists of members with varying backgrounds and appropriate professional competencies as necessary to review the effect of the research plan on an individual's privacy rights and related interests. The board must include at least one member who is not affiliated with the covered entity, is not affiliated with any entity conducting or sponsoring the research, and is not related to any person who is affiliated with any such entities. A Privacy Board cannot have any member participating in a review of any project in which the member has a conflict of interest.

Protected Health Information. PHI is individually identifiable health information transmitted by electronic media, maintained in electronic media, or transmitted or maintained in any other form or medium. PHI excludes individually identifiable health information in education records covered by the Family Educational Rights and Privacy Act, as amended, 20 U.S.C. 1232g, records described at 20 U.S.C. 1232g(a)(4)(B)(iv), and employment records held by a covered entity in its role as employer.

Research. A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. This includes the development of research repositories and databases for research.

Use. With respect to individually identifiable health information, the sharing, employment, application, utilization, examination, or analysis of such information within the entity or health care component (for hybrid entities) that maintains such information.

Waiver or Alteration of Authorization. The documentation that the covered entity obtains from an investigator or an IRB or a Privacy Board that states that the IRB or Privacy Board has waived or altered the Privacy Rule's requirement that an individual must authorize a covered entity to use or disclose the individual's PHI for research purposes.

Workforce. Employees, volunteers, trainees, and other persons whose conduct, in the performance of work for a covered entity, is under the direct control of the covered entity, whether or not they are paid by the covered entity.

23.2 The IRB's Role under the Privacy Rule

Under the Privacy Rule, IRBs gained authority to consider, and act upon, requests for a partial or complete waiver or alteration of the Privacy Rule's Authorization requirement for uses and disclosures of PHI for research. Although DHHS and FDA Protection of Human Subjects Regulations include protections to help ensure the privacy of subjects and the confidentiality of information, the Privacy Rule supplements these protections by requiring covered entities to

implement specific measures to safeguard the privacy of PHI. If certain conditions are met, an IRB may grant a waiver or an alteration of the Authorization requirement for research uses or disclosures of PHI.

University of Virginia has designated the University of Virginia IRB-HSR to fulfill the functions of a Privacy Board for human subject research.

The Privacy Rule does not change the composition of an IRB. The Privacy Rule permits a covered entity to accept documentation of waiver or alteration approval from any qualified IRB or Privacy Board -- not only the IRB overseeing the organization's research. When acting upon a request to waive or alter the Authorization requirement, an IRB must follow the procedural requirements of the DHHS Protection of Human Subjects regulations and, if applicable, FDA regulations, including using either the normal review procedures (review by the convened IRB) or the expedited review procedures.

When a request for a waiver or an alteration of the Authorization requirement is considered by the convened IRB, a majority of the IRB members must be present at the meeting, including at least one member whose primary concerns are in nonscientific areas. In order for an approval of a waiver or an alteration of the Privacy Rule's Authorization requirement to be effective, it must be approved by a majority of the IRB members present at the convened meeting. If a member of the IRB has a conflicting interest with respect to the PHI use and disclosure for which a waiver or an alteration approval is being sought, that member may not participate in the final discussion or vote. DHHS and FDA have established categories of research that may be reviewed by an IRB through an expedited review procedure. Expedited review of a request for a waiver or an alteration of the Authorization requirement is permitted where the research activity is on the DHHS or FDA list of approved categories and involves no more than minimal risks. In addition, 45 CFR 46.110 and 21 CFR 56.110 permit an IRB to use an expedited review procedure to review minor changes in previously approved research. A modification to a previously approved research plan, which only involves the addition of an Authorization for the use or disclosure of PHI to the IRB-approved informed consent, may be reviewed by the IRB through an expedited review procedure, because this type of modification may be considered to be no more than a minor change to research. If expedited review procedures are appropriate for acting on the request, the review may be carried out by the IRB Chair or by one or more experienced reviewers designated by the Chair from among the IRB members. A member with a conflicting interest may not participate in an expedited review. If an IRB uses expedited review procedures, it must adopt methods for keeping all its members advised of requests for waivers or alterations of the Authorization requirement as well as those requests that have been granted under an expedited review procedure. IRB documentation of approval of a waiver or alteration of the authorization requirement includes:

- The identity of the approving IRB
- The date on which the waiver or alteration was approved
- A statement that the IRB has determined that all the specified criteria for a waiver or an alteration were met

- A brief description of the PHI for which use or access has been determined by the IRB to be necessary in connection with the specific research activity
- A statement that the waiver or alteration was reviewed and approved under either normal or expedited review procedures
- The required signature of the IRB Chair or the Chair's designee.

Investigators will not use or disclose PHI for research without individual authorization or proper documentation of an IRB or Privacy Board approval of a waiver or alteration of the requirement, or as otherwise allowed by applicable law.”

23.3 Authorization

Except as otherwise permitted, the Privacy Rule requires that a research subject “authorize” the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject’s consent to participate in research, which is required under the Common Rule and FDA regulations. Just as a valid consent under Common Rule and FDA regulations must meet certain requirements, a valid authorization must contain certain statements and core elements [45 CFR 164.508(c)]. At University of Virginia, authorization language is to be included in a separate HIPAA Authorization or incorporated into the consent document. Template consent documents, which include HIPAA authorization language, are available from the Protocol Builder.

Once executed, a signed copy must be provided to the individual providing authorization. Signed authorizations must be retained by the covered entity for 6 years from the date of creation or the date it was last in effect, whichever is later.

A research subject has the right to revoke their authorization at any time. Investigators are not required to retrieve information that was disclosed under the authorization before learning of the revocation. Additionally, investigators may continue to use and disclosure PHI already obtained for the research under an authorization to the extent necessary to protect the integrity of the research.

When an authorization is obtained for research purposes, the Privacy Rule requires that it pertain only to a specific research study, not to nonspecific research or to future, unspecified projects. The Privacy Rule considers the creation and maintenance of a research repository or database as one specific research activity, the subsequent use or disclosure by a covered entity of information from the database for a specific research study requires separate authorization unless a waiver of the requirement is granted.

When an Authorization permits disclosure of PHI to a person or organization that is not a covered entity (such as a sponsor or funding source), the Privacy Rule does not continue to protect the PHI disclosed to such entity. However, other federal and state laws and agreements between the covered entity and recipient may establish continuing protections for the

disclosed information. Under the DHHS Protection of Human Subjects regulations or the FDA Protection of Human Subjects regulations, an IRB may impose further restrictions on the use or disclosure of research information to protect subjects.

Authorization Core Elements:

1. A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner.
2. The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure.
3. The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure.
4. A description of each purpose of the requested use or disclosure.
5. Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure (“end of the research study” or “none” are permissible for research, including for the creation and maintenance of a research database or repository).
6. Signature of the individual and date. If the individual’s legally authorized representative signs the Authorization, a description of the representative’s authority to act for the individual must also be provided.

Authorization Required Statements:

1. A statement of the individual’s right to revoke his/her Authorization and how to do so, and, if applicable, the exceptions to the right to revoke his/her Authorization or reference to the corresponding section of the covered entity’s notice of privacy practices.
2. Whether treatment, payment, enrollment, or eligibility of benefits can be conditioned on Authorization, including research-related treatment and consequences of refusing to sign the Authorization, if applicable.
3. A statement of the potential risk that PHI will be re-disclosed by the recipient. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.

23.4 Waiver or Alteration of the Authorization Requirement

Obtaining signed authorization to access and use of PHI for research is not always feasible. The Privacy Rule contains criteria for waiver or alterations of authorization. If a covered entity has used or disclosed PHI for research pursuant to a waiver or alteration of authorization, documentation of the approval of the waiver or authorization must be retained for 6 years from the date of its creation or the date it was last in effect, whichever is later.

For research uses and disclosures of PHI, an IRB or Privacy Board may approve a waiver or an alteration of the authorization requirement in whole or in part. A complete waiver occurs when the IRB or Privacy Board determines that no authorization will be required for a covered entity to use and disclose PHI for a particular research project. A partial waiver of authorization occurs when the IRB or Privacy Board determines that a covered entity does not need authorization for all PHI uses and disclosures for research purposes, such as accessing PHI for research recruitment purposes. An IRB or Privacy Board may also approve a request that removes some PHI, but not all, or alters the requirements for an authorization (an alteration).

In order for an IRB or Privacy Board to waive or alter authorization, the Privacy Rule (45 CFR 164.512(i)(2)(ii)) requires the IRB or Privacy Board to determine the following:

1. The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
 - a. An adequate plan to protect health information identifiers from improper use and disclosure.
 - b. An adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a healthcare or research justification for retaining them or a legal requirement to do so).
 - c. Adequate written assurances that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.
2. The research could not practicably be conducted without the waiver or alteration.
3. The research could not practicably be conducted without access to and use of the PHI.

The Privacy Rule allows institutions to rely on a waiver or an alteration of Authorization obtained from a single Privacy Board to be used to obtain or release PHI in connection with a multi-site project.

23.5 Activities Preparatory to Research

Under the preparatory to research provision of the Privacy Rule, a covered entity may permit an investigator who works for that covered entity to use PHI for purposes preparatory to research such as assessing the feasibility of conducting a research project, developing a grant application, or identifying potential subjects. A covered entity may also permit, as a disclosure of PHI, a researcher who is not a workforce member of that covered entity to review PHI (within that covered entity) for purposes preparatory to research.

The covered entity must obtain from an investigator representations that (1) the use or disclosure is requested solely to review PHI as necessary to prepare a research plan or for similar purposes preparatory to research, (2) the PHI will not be removed from the covered entity in the course of review, and (3) the PHI for which use or access is requested is necessary for the research.

At University of Virginia, this is accomplished by the investigator submitting either a Preparatory to Research form (for projects in development) to the Health Information Services Office.

23.6 Research Using Decedent's Information

The Health Information Services Office obtains from the investigator:

(A) Representation that the use or disclosure sought is solely for research on the protected health information of decedents; (B) Documentation, at the request of the covered entity, of the death of such individuals; and (C) Representation that the protected health information for which use or disclosure is sought is necessary for the research purposes.

23.7 Future Uses: Databases and Repositories

The Privacy Rule recognizes the creation of a research database or a specimen repository to be a research activity if the data/specimens to be stored contain PHI. There are two separate activities that the covered entity must consider: (1) the use or disclosure of PHI for creating a research database or repository and (2) the subsequent use or disclosure of PHI in the database for a particular research plan.

Individual authorization for the storage of PHI for future research must be sought unless the IRB has determined that the criteria for a waiver of the authorization requirement are satisfied. See Section 23.4 of this policy manual for a discussion of waivers of authorization.

At University of Virginia, consent for research and authorization for use and/or disclosure of PHI may be combined in one document. As with any research activity, the combined consent/authorization for future research must describe the future research uses in sufficient detail to allow the potential subject to make an informed decision. The investigator and IRB should be cognizant of uses of information/specimens that the target community may consider particularly sensitive, such as genetics, mental health, studies of origin, and use of tissues that may have cultural significance.

The consent/authorization for future research can be a stand-alone document or may be incorporated into another consent/authorization if the information/specimens will originate from another research activity, such as a clinical trial, unless the research involves the use or disclosure of psychotherapy notes. Authorizations for the use or disclosure of psychotherapy notes can only be combined with another authorization for a use or disclosure of psychotherapy notes.

If the consent/authorization for future research is combined with another research consent/authorization, the consent/authorization must clearly differentiate between the research activities and allow the individual to opt-in to the future research. Opt-outs for future research are not permitted under the Privacy Rule because an opt-out process does not provide individuals with a clear ability to authorize the use of their information/specimens for future research, and may be viewed as coercive.

23.8 Corollary and Sub-studies

As with any other research, subject participation in corollary or sub-studies not essential to the primary aims of the research should be on a voluntary basis. This is particularly important when the primary research offers a potential benefit, such as treatment, that might compel the potential subject to agree to something that they otherwise would not.

HIPAA reinforces this ethical principle by explicitly stating that authorization for “unconditioned” activities, for which there is no associated treatment, benefit or other effect on the individual subject associated with participation, cannot be required. The published preamble to HIPAA Omnibus clarifies the basis for this position, and the requirement that authorization for unconditioned activities involve a clear opt-in mechanism, stating:

“This limitation on certain compound authorizations was intended to help ensure that individuals understand that they may decline the activity described in the unconditioned authorization yet still receive treatment or other benefits or services by agreeing to the conditioned authorization.” and “an opt out option does not provide individuals with a clear ability to authorize the optional research activity, and may be viewed as coercive by individuals.”

As with authorization for future research, it is acceptable to combine in a single document the authorization for a conditioned activity, such as a clinical trial, with authorization for an unconditioned activity such as a corollary or sub-study that does not directly benefit the individual participant, provided that:

1. The authorization clearly differentiates between the conditioned and unconditioned research activities;
2. The authorization clearly allows the individual the option to opt in to the unconditioned research activities; and
3. Sufficient information is provided for the individual to be able to make an informed choice about both the conditioned and unconditioned activities.

Separate authorization must be obtained for each research activity that involves the use and disclosure of psychotherapy notes. For example, authorization for the use and disclosure of psychotherapy notes for a clinical trial cannot be combined with an authorization for the use and disclosure of those psychotherapy notes for a corollary research activity.

23.9 De-identification of PHI under the Privacy Rule

Covered entities may use or disclose health information that is de-identified without restriction under the Privacy Rule. The “Safe Harbor” method permits a covered entity to de-identify data by removing all 18 data elements that could be used to identify the individual or the individual’s relatives, employers, or household members. The covered entity also must have no actual knowledge that the remaining information could be used alone or in combination with other information to identify individuals. Under this method, the identifiers that must be removed are the following:

- 1) Names.
- 2) All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:
 - a. The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people.
 - b. The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.
- 3) All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.
- 4) Telephone numbers.
- 5) Facsimile numbers.
- 6) Electronic mail addresses.
- 7) Social security numbers.
- 8) Medical record numbers.
- 9) Health plan beneficiary numbers.
- 10) Account numbers.
- 11) Certificate/license numbers.
- 12) Vehicle identifiers and serial numbers, including license plate numbers.
- 13) Device identifiers and serial numbers.
- 14) Web universal resource locators (URLs).
- 15) Internet Protocol (IP) address numbers.
- 16) Biometric identifiers, including fingerprints and voiceprints.
- 17) Full-face photographic images and any comparable images.

- 18) Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.

Alternatively, a qualified statistician may certify that the risk is very small that health information could be used, alone or in combination with other available information, to identify individuals. The qualified statistician must document the methods and results of the analysis that justify such a determination. This analysis must be retained by the covered entity for 6 years from the date of its creation or when it was last acted on, whichever is later.

The Privacy Rule permits a covered entity to assign to, and retain with, the de-identified health information, a code or other means of record re-identification if that code is not derived from or related to the information about the individual and is not otherwise capable of being translated to identify the individual. The covered entity may not use or disclose the code or other means of record identification for any other purpose and may not disclose its method of re-identifying the information.

NOTE: Data that is considered de-identified under HIPAA may still be considered human subject data under the Common Rule, particularly when working with a small data set that can be further divided into smaller subsets. Additionally, while coded information may be de-identified under HIPAA, if the investigator holds or has the ability to access both the code and the data, the information is considered identifiable private information under the Common Rule.

23.10 Limited Data Sets and Data Use Agreements

Limited data sets are data sets stripped of certain direct identifiers. Limited data sets may be used or disclosed only for public health, research, or health care operations purposes. Because limited data sets may contain identifiable information, they are still PHI and as such are not considered de-identified under the Privacy Rule. Unlike de-identified data, protected health information in limited data sets may include: addresses other than street name or street address or post office boxes, all elements of dates (such as admission and discharge dates) and unique codes or identifiers not listed as direct identifiers. The following direct identifiers must be removed for PHI to qualify as a limited data set:

- 1) Names;
- 2) postal address information, other than town or city, state, and ZIP code;
- 3) telephone numbers;
- 4) fax numbers;
- 5) email addresses;
- 6) social security numbers;
- 7) medical record numbers;
- 8) health plan beneficiary numbers;

- 9) account numbers;
- 10) certificate or license numbers;
- 11) vehicle identifiers and license plate numbers;
- 12) device identifiers and serial numbers;
- 13) URLs;
- 14) IP addresses;
- 15) biometric identifiers; and
- 16) full-face photographs and any comparable images.

23.11 Disclosing a Limited Data Set

Before disclosing a limited data set, a covered entity must enter into a data use agreement (DUA) with the recipient, even when the recipient is a member of its workforce. The data use agreement establishes the parameters around the proposed uses and disclosures of the data, who is permitted to have access to the data, and stipulates that no other use will be made of the data, no attempt will be made to identify or contact individuals whose data are included in the limited data set, that appropriate safeguards are in place to protect the data from unauthorized use and that the recipient will report any uses or disclosures of the PHI that they become aware of that not in keeping with the terms of the DUA. Data Use Agreements for the purposes of research are available through the Office of Sponsored Programs or the IRB-HSR office.

Research Subject Access to PHI

With few exceptions, the Privacy Rule guarantees individuals access to their medical records and other types of health information. One exception is during a clinical trial, when the subject's right of access can be suspended while the research is in progress. The subject must have been notified of and agreed to the temporary denial of access when providing consent and authorization. Any such notice must also inform the individual that the right to access will be restored upon conclusion of the clinical trial. Language accommodating this exclusion is included in the applicable University of Virginia research consent/authorization templates.

23.12 Accounting of Disclosures

The Privacy Rule generally grants individuals the right to a written "Accounting of Disclosures" of their Protected Health Information made by a covered entity without the individual's authorization in the six years prior to their request for an Accounting. A covered entity must therefore keep records of such PHI disclosures for 6 years.

It is important to understand the difference between a use and a disclosure of PHI. In general, the use of PHI means communicating that information within the covered entity. A disclosure of PHI means communicating that information to a person or entity outside the covered entity.

The Privacy Rule restricts both uses and disclosures of PHI, but it requires an accounting only for certain PHI disclosures.

Generally, an Accounting of Disclosures is required for:

- 1) Routinely Permitted Disclosures (e.g., under public health authority, to regulatory agencies, to persons with FDA-related responsibilities) with limited exceptions (e.g., law enforcement, national security, etc.)
- 2) Disclosures made pursuant to:
 - a. Waiver of Authorization
 - b. Research on Decedents' Information
 - c. Reviews Preparatory to Research

An accounting is not needed when the PHI disclosure is made:

- 1) For treatment, payment, or health care operations.
- 2) Under an Authorization for the disclosure.
- 3) To an individual about himself or herself.
- 4) As part of a limited data set under a data use agreement.

The Privacy Rule allows three methods for accounting for research-related disclosures that are made without the individual's Authorization or other than a limited data set: (1) A standard approach, (2) a multiple-disclosures approach, and (3) an alternative for disclosures involving 50 or more individuals. Whatever approach is selected, the accounting is made in writing and provided to the requesting individual. Accounting reports to individuals may include results from more than one accounting method.

Additional information may be found at the [University of Virginia Medical Center Policy No. 0256: Accounting of Disclosures](#)

24. Information Security

University of Virginia has established standards and safeguards to protect patient's information and to ensure compliance with federal and state information security regulations. It is the responsibility of investigators to familiarize themselves with and comply with these standards which may be found on the [Information Security \(InfoSec\) website](#). The use of individual use devices such as personal laptops, desktops, portable/USB drives, or other non-University of Virginia devices for storage of research data is discouraged. In the instances when an individual use device or a non-University of Virginia computer or device must be used for the purposes of storing, even temporarily, or transmitting PHI or PII (Personally Identifiable Information) for research, the safeguards of the device must be verified by InfoSec and the study team must submit the Highly Sensitive Data Storage Request form. This form requires the signatures of a Department Manager or Chair and a VP or Dean. Additionally, any potential or known breach of a device or of research data must be immediately reported according to the [Information Security Incident Reporting Policy](#) so that appropriate steps can be taken to assess the situation, protect the information, and comply with regulations. Any data breach will also be reported to the IRB of Record if the report meets the criteria of an [Unanticipated Problem](#).

Provisions for Data Security must be described in Data Security Plan to the IRB and updated as necessary. When information containing direct identifiers such as Social Security numbers or PHI including data considered sensitive is to be transferred outside of the institution, the provisions for data security may be subject to further review by InfoSec.

25 Special Topics

(RESERVED)

25.1 Community Based Research

Community based research (CBR) is research that is conducted as an equal partnership between academic investigators and members of a community. In CBR projects, the community participates fully in all aspects of the research process. *Community* is often self-defined, but general categories of community include geographic community, a community of individuals with a common problem or issue, or a community of individuals with a common interest or goal.

Where research is being conducted in communities, investigators are encouraged to involve members of the community in the research process, including the design and implementation of research and the dissemination of results when appropriate. The HRPP Office will assist the investigator in developing such arrangements.

The most significant community involvement is in a subset of CBR called Community Based Participatory Research (CBPR) where there is an equal partnership between the academic investigators and members of a community, with the latter actively participating in all phases of the research process including the design and implementation of research and the dissemination of results when appropriate.

Questions to be considered as CBR studies are developed, and issues that the IRB will consider when reviewing CBR are as follows:

- How was the community involved or consulted in defining the need for the proposed research (i.e., getting the community's agreement to conduct the research)?
- How was the community involved or consulted in generating the study research plan?
- How will the research procedures, including recruitment strategies and consent processes be assessed to ensure sensitivity and appropriateness to various communities (e.g., literacy issues, language barriers, cultural sensitivities, etc.)?
- How will the community be involved in the conduct of the proposed research?
- How will community members who participate in the implementation of the research be trained and supervised?
- How have "power" relationships between investigators and community members on the research team, and in subject recruitment strategies been considered to minimize coercion and undue influence?
- What are the risks and benefits of the research for the community as a whole?
- How will boundaries between multiple roles (e.g., investigator, counselor, peer) be maintained, i.e., what happens when the investigator/research staff is the friend, peer, service provider, doctor, nurse, social worker, educator, funder, etc.)

- How will the research outcomes be disseminated to the community?
- Is there a partnership agreement or memorandum of understanding to be signed by the University of Virginia investigator and community partners that describes how they will work together?

When CBR studies are proposed, the above information will be included in the submission materials. When the IRB reviews CBR studies, it will include, either as members or consultants, individuals with expertise in community based research.

25.2 International (Transnational) Research

The IRB will review all International (transnational) research involving human participants to assure adequate provisions are in place to protect the rights and welfare of the participants.

Approval of research is permitted if “the procedures prescribed by the foreign institution afford protections that are at least equivalent to those provided in 45 CFR 46.”

All policies and procedures that are applied to research conducted domestically should be applied to research conducted in other countries, as appropriate.

For International research, the University of Virginia IRB seeks sufficient knowledge of the local research context by requesting approval for the project from local IRBs or ethics committees (which may or may not be OHRP-registered) and/or local letters of support. The source of this information will depend on the nature of the study, on the country and on the resources available to the investigator. Where there is a local IRB/IEC, University of Virginia IRB must receive the name and FWA# of each local IRB with the IRB submission. The PI will be responsible for obtaining the local IRB approval for each site prior to the enrollment of subjects at that site.. The Office of Sponsored Programs will verify the IRB approval is on file prior to signing the sub-contract with each site.

In some circumstances where research may be performed internationally and/or in settings where there are no IRBs, the University of Virginia IRB may, prior to approval of the research, require additional verification and information from people outside the particular research project who are familiar with the customs, practices, or standards of care where the research will be taking place, such as local IRBs or ethics committees, other University of Virginia investigators with knowledge of the region, or a consultant who is an expert on the region. These individuals may either provide a written review of a particular research plan or attend an IRB meeting to provide the University of Virginia IRB with recommendations based on his or her expertise.

For Federally funded research, approval of research for foreign institutions or sites “engaged” in research is only permitted if the foreign institution or site holds an Assurance with OHRP and local IRB review and approval is obtained.

Approval of research for foreign institutions or sites “not engaged” in research is only permitted if one or more of the following circumstances exist:

- When the foreign institution or site has an established IRB/IEC, the investigator must obtain approval to conduct the research at the "not engaged" site from the site's IRB/IEC or provide documentation that the site's IRB/IEC has determined that approval is not necessary for the investigator to conduct the proposed research at the site.
- When the foreign institution or site does not have an established IRB/IEC, a letter of cooperation must be obtained demonstrating that the appropriate institutional or oversight officials permit the research to be conducted at the performance site.
- Enrollment of subjects at the foreign institution or site is contingent upon the UVA PI receiving documentation of the performance site's IRB/IEC determination, or letter of cooperation, as applicable.

25.2.1.1 IRB Responsibilities

In addition to standard IRB review, the IRB will consider the following in the review of international research:

1. The investigator and research staff are qualified to conduct research in that country including knowledge of relevant laws, regulations, guidance and customs.
2. The consent process and consent documents are appropriate for the languages of the subjects and communication with the subject population. Arrangements are considered to communicate with the subjects throughout the study (e.g., to answer questions).
3. The IRB considers how modifications to the research will be handled. The IRB and investigators should consider as many contingencies (e.g., survey questions) as possible when research is reviewed and approved.
4. The IRB considers how complaints, non-compliance, protocol/research plan deviations and unanticipated problems involving risks to participants or other are handled.
5. The IRB considers how post-approval monitoring will be conducted.
6. The IRB considers if the investigator has obtained the appropriate host country permissions to conduct research (e.g., institutional, governmental or ministerial, IRB, local or tribal). When appropriate, the IRB communicates and coordinates with the local institutions or ethics committees.
7. The IRB considers mechanisms for communicating with the investigators and research staff when they are conducting the research in other countries.

25.2.1.2 Investigator Responsibilities

1. It is the responsibility of University of Virginia investigator and the foreign institution or site to assure that the resources and facilities are appropriate for the nature of the research.

2. It is the responsibility of University of Virginia investigator and the foreign institution or site to confirm the qualifications of the investigators and research staff for conducting research in that country(ies).
3. Investigators obtain all appropriate host country permissions to conduct research (e.g., institutional, governmental or ministerial, IRB, local or tribal).
4. It is the responsibility of University of Virginia investigator and the foreign institution or site to ensure that the consent process and consent document are appropriate for the languages of the subjects and communication with the subject population. Arrangements are considered to communicate with the subjects throughout the study (e.g., to answer questions).
5. It is the responsibility of University of Virginia investigator and the foreign institution or site to ensure that the following activities will occur.
 - a. Initial review, continuing review, and review of modification
 - b. Post-approval monitoring
 - c. Handling of complaints, non-compliance and unanticipated problems involving risk to subjects or others.
6. The IRB will not rely on a local ethics committee that does not have policies and procedures for the activities listed above.
7. Investigators will consider how complaints, non-compliance, protocol/research plan deviations and unanticipated problems involving risks to participants or other are communicated to the IRB.
8. It is the responsibility of University of Virginia investigator and the foreign institution or site to notify the IRB promptly if a change in research activities alters the performance site's engagement in the research (e.g., performance site "not engaged" begins to obtain consent of research participants, etc.).
9. Investigators cooperate with the IRB regarding how and when post-approval monitoring will be conducted.
10. Investigators consider mechanisms for communicating with the IRB when they are conducting the research in other countries.

25.2.1.3 Consent Documents

The informed consent documents must be in a language understandable to the proposed participants. Therefore, the IRB of Record will review either a document confirming the translation by a certified translator, a back translation of the consent, or review of the consent by an IRB member who is fluent in both languages confirming the accuracy of the translation. Any documents confirming the accuracy of the translation must be placed in the IRB file.

25.2.1.4 Monitoring of Approved International Research

If the overall PI of the protocol is a UVA faculty or staff member or the PI of the grant, the UVA IRB is responsible for the ongoing review of international research conducted under its jurisdiction in accordance with all applicable federal regulations. The IRB application will include a plan to monitor the study. This may include a plan from the UVA PI to monitor the

study, monitoring to be performed by an outside sponsor or confirmation of a post approval monitoring plan from the research site. A summary of the monitoring activities will be submitted with the continuation status report.

25.3 Research Involving Data and/or Biological Specimens

25.3.1 Overview

Storing data and/ or biological specimens for research and the use of data and/or biological specimens in research may require IRB approval (or exemption) and informed consent for any of the following:

- Data and/or biological specimens collected for research purposes
- Data and/or specimens collected, stored, and/or distributed for *future research uses*
- Previously collected data/specimens used for *secondary research*.

25.3.2 Definitions

Anonymous: Unidentified (i.e., personally identifiable information was not collected, or if collected, identifiers were not retained and cannot be retrieved); information or materials (e.g., data or specimens) that cannot be linked directly or indirectly *by anyone* to their source(s).

Coded: Direct personal identifiers have been removed (e.g., from data or specimens) and replaced with words, letters, figures, symbols, or a combination of these (not derived from or related to the personal information) for purposes of protecting the identity of the source(s); but the original identifiers are retained in such a way that they can be traced back to the source(s) by someone with the code. *Note: A code is sometimes also referred to as a “key,” “link,” or “map.”*

De-identified: All direct personal identifiers are *permanently* removed (e.g., from data or specimens), no code or key exists to link the information or materials to their original source(s), and the remaining information cannot reasonably be used *by anyone* to identify the source(s). *Note: For purposes of HRPP SOP, protected health information (PHI) is de-identified when it does not contain any of the 18 identifiers specified by the Health Insurance Portability and Accountability Act (HIPAA) at 45 CFR Part 164 or has been determined to be de-identified by a statistician in accordance with the standards established by the Privacy Rule. For more information, including the list of identifiers that must be removed to de-identify health information, see [HIPAA and Human Subjects Research](#).*

Repository: Also: **bank, database.** Collection of data and/or specimens obtained and stored for future research uses and/or distribution, including a collection not originally or primarily obtained for research purposes.

Specimen: Also: **sample.** Human biological material includes sub-cellular components such as DNA or RNA, Gametes (e.g., ova and sperm), embryos and fetal tissue, breast milk,

exhaled air, including solid material (e.g., tissue, organs), body products (e.g., teeth, hair, nail clippings, sweat, urine, feces, saliva, semen, cerebrospinal fluid), blood and blood fractions (e.g. plasma, serum, buffy coat, red blood cells) and cells. Exceptions include organisms, such as bacteria and viruses isolated from human specimens are not human biological specimens

Leftover/Remnant Specimen: Remaining portion of a specimen obtained for clinical purposes that is no longer needed for its original purpose and that would otherwise be discarded.

Secondary Research: Study of existing information or materials (e.g., data or specimens) that have been previously collected for a purpose (including non-research purposes) other than the currently proposed activity.

25.3.3 General Information

Prospective collection of data and/or specimens for research purposes (e.g., additional questions added to routine surveys being performed for non-research purposes, an extra tube of blood taken at the time of clinical blood drawing, etc.) is “research involving human subjects,” and IRB review and approval is required. Informed consent (and HIPAA authorization for data that include PHI) must also be obtained.

Collection and storage of data and/or specimens for *future research uses* and/or distribution (i.e., rather than using data/specimens only for pre-defined analyses as described in a specific IRB-approved protocol) are activities that meet the definition of “research involving human subjects,” and IRB review and approval is required (see “Repositories – Collection, Storage, and/or Distribution of Data/Specimens” below). Informed consent (and HIPAA authorization for data that include PHI) is also required.

When the data and/or specimens to be stored for future research uses are generated as part of another research study (e.g., clinical trial), a separate protocol describing repository activities must generally be submitted for IRB review and approval before the protocol that collected the data and/or specimens is closed, unless the bank is externally controlled (see “Repositories – Collection, Storage, and/or Distribution of Data/Specimens” below). *Note: Sponsor-mandated data sharing may not require a stand-alone repository submission.*

In some cases, secondary uses of previously collected data and/or specimens meet the definition of “research involving human subjects,” and IRB approval or exemption is required (see “Secondary Uses of Previously Collected Data/Specimens” below).

Certain activities involving data and/or specimens do not meet the definition of “research involving human subjects” and do not require IRB approval or exemption, as described below.

25.3.4 Activities That Are Not Human Subjects Research

Laboratory research with *commercially available* tissue specimens, cell lines, or other human cells does not meet the definition of “research involving human subjects” and may be performed without IRB approval or exemption as long as the work is not FDA-regulated (see “Research Subject to FDA Regulations” below).

Research with *autopsy* specimens does not meet the definition of “research involving human subjects” and may be performed without IRB approval or exemption. Research involving decedents’ PHI is subject to HIPAA regulations. HIPAA authorization (or waiver) is generally not required for use or disclosure of PHI for research involving decedents only, with appropriate representations from the researcher. For more information, contact the UVA Health System Privacy Officer at 434-924-5024.

Research with previously collected *anonymous* (see “Definitions” above) data and/or specimens does not meet the definition of “research involving human subjects” and may be performed without IRB approval or exemption *only* when the data/specimens to be studied were not collected specifically for the current research. Note: An investigator may not de-identify data and/or specimens under his or her control (e.g., data collected by the investigator for another study) for future research uses without IRB review.

Research with previously collected *coded* data and/or specimens does not meet the definition of “research involving human subjects” and may be performed without IRB approval or exemption *only* when **all** of the following conditions are met:

- The data and/or specimens to be studied were not collected specifically for the current research
 - Investigator(s) cannot “readily ascertain” the identity of the source(s) of the coded data or specimens because one or more of the conditions below is met:
 - 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 source individuals are deceased)
 - IRB-approved written policies and procedures for the repository or data coordinating center prohibit the release of the key to the investigators under any circumstances (until the source individuals are deceased).

Research with *leftover* specimens does not meet the definition of “research involving human subjects” and may be performed without IRB approval or exemption *only* when their use meets the conditions for *anonymous* or *coded* specimens above. Note: An investigator may not de-identify data and/or specimens under his or her control (e.g., specimens generated by the investigator from a clinical procedure) for future research uses without IRB review.

The research uses of previously collected data and/or specimens described above *may* be defined as “research involving human subjects” under FDA regulations and may require IRB approval and participant informed consent, depending on the nature of the research (see “Research Subject to FDA Regulations” below).

25.3.5 Exempt Research

Research involving *existing* data and/or specimens is exempt when **all** of the following conditions are met:

- All data and/or specimens are available, or “on the shelf,” at the time the research is submitted for an exempt determination
- The sources of the data and/or specimens are publicly available or the information is recorded by the investigator in a way that participants cannot be identified, directly or through identifiers linked to the participants
- The research is not subject to FDA regulations.

Note: An investigator may not de-identify data and/or specimens under his or her control (e.g., data collected by the investigator for another purpose or study) for future research uses without IRB review.

Prospective collection of biological specimens is not exempt from IRB review. Prospective data collection may be exempt in certain cases (e.g., some research qualifying under exempt category #1), depending on the nature of the data and population from whom the information is collected. For more information see HRPP SOP [[Exempt Research](#)].

25.3.6 Secondary Uses of Previously Collected Data/Specimens

IRB approval or exemption is required for secondary research uses of previously collected data and/or biological specimens, unless only *anonymous* or *coded* data/specimens are used as described above (see “Activities That Are Not Human Subjects Research”).

Secondary research uses of *non-research* collections of data/specimens (e.g., data or specimens that are retained for purposes other than research, such as clinical or educational records, archived pathology specimens, etc.) require IRB approval or exemption, as such collections have not been established as repositories with IRB-approved procedures for releasing materials that consider human subjects protection requirements.

Secondary (i.e., “new”) uses of data/specimens obtained for *primary research purposes* by an investigator with IRB approval (or exemption) require IRB review of an amendment or a new protocol describing the proposed secondary use, depending on the previous approval (or exemption) and the new research objective(s). Informed consent may also be required for this new use (as described below), depending on the scope of the original consent and the newly proposed research.

Research using previously collected data and/or specimens must be consistent with the scope and terms described in the original informed consent process/document, as applicable. If consent was not obtained (e.g., data/specimens obtained for non-research purposes) or the original consent does not adequately include the proposed secondary use, specific informed consent for the new research may be required. De-identification or coding of data/specimens should not be used as a means for circumventing the original terms of consent. Except in unusual circumstances, informed consent is required when identifiable data and/or specimens are used.

Informed consent (and HIPAA authorization, when applicable) can be waived by the IRB for minimal risk non-exempt research with previously collected data and/or specimens when the research meets the regulatory criteria for waiver (see “Informed Consent Requirements” below).

Protocols for using previously collected data and/or biological specimens for research purposes should include the following information, as applicable:

- Purpose of using data/specimens
- Type(s) of data/specimens to be studied
- Source(s) and circumstances under which the data/specimens were collected
- State of the data/specimens to be obtained (i.e., identifiable or coded)
- If the data include individually identifiable protected health information
- Whether informed consent (and HIPAA authorization, when applicable) was obtained for collection and future use of data/specimens
- Physical location/equipment and security provisions for data/specimen storage
- Plan for destruction or de-identification of identifiable or coded data/specimens at the end of the retention period.

Investigators may not share data and/or specimens with collaborators (internal or external to UVA) for secondary research purposes without IRB approval. Distribution of data and/or specimens for secondary research uses beyond a single transfer described in a specific IRB-approved protocol generally requires approval for a repository (see “Repositories – Collection, Storage, and/or Distribution of Data/Specimens” below).

Confidential disclosure agreements (CDAs), data use agreements (DUAs), or material transfer agreements (MTAs) may be required for sharing research data or specimens with non-UVA collaborators. For more information and signatory authority, see or contact the UVA OSP office or the School of Medicine Grants and Contracts Office if within the School of Medicine

Access to and/or use of identifiable patient information from medical records or clinical databases for research purposes must comply with the requirements of the HIPAA Privacy

and Security Rules and university policy [e.g., [University Hospital Policy 09-11: Use of Patient Information by Hospitals and Medical Staff](#)]. For more information, contact the UVA Health System Privacy Officer at 434-924-5024.

The proposed use of student education records in research must comply with the requirements of the [Family Educational Rights and Privacy Act \(FERPA\)](#). For information about the release of student records at UVA, see [Privacy and Release of Student Education Records](#) or contact the Office of the IRB for Social & Behavioral Research at 434-243-2915 or the Office of the University Registrar at 434-924-4122.

25.3.7. Repositories – Collection, Storage, and/or Distribution of Data/Specimens

Data and specimen repositories/banks may range from materials held by a single investigator in his/her office or laboratory to large networks with central coordinating centers. Although the size, purpose, types of information and materials stored, and populations from whom the data/specimens are collected may also vary widely, creating a data and/or specimen bank for *future research purposes* (i.e., rather than using data/specimens only for pre-defined analyses as described in a specific IRB-approved protocol) is defined as “research involving human subjects;” and IRB review and approval is required.

Informed consent is required for collection of data and/or biological specimens to be stored for future research (see “Informed Consent Requirements” below). HIPAA authorization is also required when the data include protected health information.

Banking should be understood as the collection and storage of biological samples for future undefined research.

Caution should be taken when requiring participants to agree to the banking of their tissue for future undefined research or for research unrelated to the study at hand as a condition for entry into a trial that offers the potential participant the prospect of some direct benefit. Mandatory banking may be more acceptable if the future research will be related to disease process under study.

The final determination as to whether the proposed mandatory banking for future unrelated research is acceptable will be made by the IRB on a case by case basis.

Protocols for creating data and/or biological specimen repositories for research purposes should include the following information, as applicable:

- Purpose of collecting and storing data/specimens
- Type(s) of data/specimens to be collected and stored

- Source(s) and circumstances of data/specimen collection (i.e., obtained directly from participants or from a secondary source)
- How the data/specimens will be stored (i.e., identifiable, coded, or de-identified)
- If the data include individually identifiable protected health information
- Physical location/equipment and security provisions for data/specimen storage
- Length of time data/specimens will be stored
- Any limits on data/specimens' intended future use (e.g., for cancer research only)
- With whom data/specimens may be shared (including non- UVA researchers)
- Process for requesting and releasing data/specimens
- How data/specimens will be released (i.e., identifiable, coded, or de-identified)
- Procedures to withdraw participants' data/specimens from future research
- Plan for continuing repository operations in the absence (or departure) of the principal investigator
- Process for destruction or de-identification of identifiable or coded data/specimens at the end of the retention period.

Consideration should be given to obtaining a National Institutes of Health (NIH) Certificate of Confidentiality to protect the confidentiality of banked identifiable or coded data/specimens. Certificates of Confidentiality are intended to protect information that, if disclosed, could have adverse consequences for research participants or damage their financial standing, employability, insurability, or reputation. Examples include information about the following:

- Sexual or gender preferences or practices,
- Misuse of alcohol, drugs, or other addictive products,
- Illegal conduct
- Sensitive information pertaining to mental illness,
- Sensitive genetic information.

For more information about Certificates of Confidentiality, see “NIH Certificates of Confidentiality” in HRPP SOP [[Privacy and Confidentiality](#)] or NIH “[Certificates of Confidentiality Kiosk](#).”

Methods for handling and storing data (including the use of personal computers and portable storage devices) must comply with university policies. Restricted data, including protected health information, must be encrypted if stored or used on portable devices, if removed from a secure university location, or if electronically transmitted. For more information, see the [UVA Electronic Data Removal Policy](#) and [UVA Electronic Storage of Highly Sensitive Data](#) Policy.

Investigators and IRBs should consider when research involving the collection and storage of personally identifiable information (i.e., information that can be used to distinguish an individual's identity, such as name, social security number, date of birth, etc., or information linked to an individual, such as medical, financial, or employment information) might expose research participants to the risk of fraud or identity theft. This is especially important in research linked to "fee-for-service" activities, where federal financial regulations for protecting consumers against identity theft may apply. In such cases, plans for handling and storing personally identifiable information must comply with university policy and Federal Trade Commission rules. For more information, see the [UVA Data Protection Standards](#).

Medical Center Policy # 0119] stipulates that unless specifically exempted from evaluation by the Operating Room Committee, all human tissue and objects/ devices obtained by surgical procedure, traumatic excision, or disease associated sequelae (e.g., vascular auto-amputation) from a patient in any area of the Medical Center, including the Main Operating room, the Outpatient Surgery Center, ambulatory clinics, the Emergency Department, and any procedural area shall be sent to the University of Virginia Department of Pathology for evaluation prior to any substantive treatment, including but not limited to, surgical procedures or radiation therapy. The Operating Room Committee does exempt the requirement for pathology examination of diagnostic surgical tissue/specimens prior to collection of these materials for research purposes if the subject has signed consent.

25.3.8. Informed Consent Requirements

Informed consent must be obtained for collection and storage of data and/or biological specimens for future research and should generally be obtained separately from consent to other research participation. HIPAA authorization is also required when the data include protected health information. For more information on the requirements for obtaining and documenting informed consent, see HRPP policies [] and [].

Investigators and IRBs should balance the ethical obligation to provide sufficient information regarding possible *future research uses* of stored data and/or specimens during the consent process for banking with the practical issues of trying to anticipate and describe all possible research uses of these materials. However, the consent process for collecting and banking data and/or specimens should be as specific as possible regarding the circumstances and any risks associated with data/specimen collection, as well as the procedures for maintaining the security and confidentiality of the stored materials. In addition to the required elements of informed consent, the consent process should include the following information, as applicable:

- Description of the data/specimens to be collected and how they will be obtained
- Any risks associated with obtaining the data/specimens
- How the data/specimens will be used (to the extent known) • Any limits on data/specimens' intended future use (e.g., for cancer research only)

- Whether any identifying information will be retained, and if so, how it will be stored
- Certificate of Confidentiality information (when a Certificate is obtained)
- Description of the repository, including physical location, security procedures, etc.
- Who will have access to the data/specimens
- How long the data/specimens will be stored
- With whom data/specimens may be shared (including non-UVA researchers)
- How to withdraw data/specimens from future research
- Whether or not participants may be re-contacted in the future (e.g., for consent to future research, to return research results, etc.).

HIPAA allows UVA to provide identifiable patient data or specimens (PHI) to a sponsor/grantor (with appropriate consent/authorization or waiver) in return for payments in the form of grants or contracts for UVA to perform research activities, because any provision of PHI to the sponsor/grantor is a byproduct of the service being provided to the sponsor/grantor. However, a disclosure of PHI to an outside entity where no research is being performed by UVA in exchange for the payment would be considered a “sale of PHI,” for which UVA must have a signed authorization from the patient that discloses the payment, unless the payment is only a reasonable cost-based fee to cover the cost to prepare and transmit the data and the PHI consists only of a “Limited Data Set” covered by a Data Use Agreement or is provided under a waiver of authorization granted by an IRB. For questions, contact the UVA Office of University Counsel at 434-924-3586.

When identifiable specimens and/or genetic information are stored and may be released for future research, the consent process/document should also include language describing the protections provided by the Genetic Information Nondiscrimination Act. For specific language, see the consent form templates from Protocol Builder.

The informed consent process/document must not include any exculpatory language through which subjects are made to waive or appear to waive any legal rights regarding the collection or use of their data and/or specimens. For more information see HRPP SOP [[Informed Consent Process and the Elements of Informed Consent](#)].

Research using previously banked data and/or specimens should be consistent with the scope and terms described in the original informed consent process/document, as applicable. If consent was not obtained (e.g., data/specimens obtained for non-research purposes) or the original consent does not adequately include the proposed secondary use, specific informed consent for the new research may be required. Except in unusual circumstances, informed consent is required when identifiable data and/or specimens are used.

Informed consent (and HIPAA authorization, when applicable) can be waived by the IRB for minimal risk non-exempt research with previously collected data and/or specimens when the research meets the regulatory criteria for waiver. Waiver of HIPAA authorization can also be granted (when applicable) by the Privacy Board for secondary uses of existing data and/or specimens in exempt research. For more information on waiver of informed consent, see HRPP SOP sections 11.9: Waiver of Informed Consent and 23: Health Insurance Portability and Accountability Act (HIPAA).

25.3.9. Research Subject to FDA Regulations

Activities involving data and/or specimens that do not require IRB approval under DHHS regulations (see “Activities That Are Not Human Subjects Research” above) must still receive IRB approval if the activities are subject to FDA regulations (e.g., involving FDA-regulated products or submission of data/results to FDA). Activities with data and/or specimens defined by FDA as “research involving human subjects” include testing of *in vitro* diagnostic devices using biological specimens and the use of clinical data for historical “controls” in investigational drug studies.

FDA regulations do not permit waivers of the informed consent requirements in research, except for emergencies (i.e., emergency use of a test article or emergency research) or in certain types of military research. However, under specific circumstances *in vitro* diagnostic device studies may be performed with biological specimens without informed consent, as described below.

FDA intends to exercise “enforcement discretion” regarding the requirements for informed consent in an *in vitro* diagnostic device study involving biological specimens when **all** of the following criteria are met:

- The study meets the IDE exemption criteria
- The study uses leftover/remnant specimens, specimens obtained from repositories, or unused specimens that were previously collected for other research purposes
- The specimens are not individually identifiable
- Clinical information accompanying the specimens does not make the specimen source identifiable
- Individuals caring for the patients from whom the specimens were obtained do not share information with the investigator(s)
- Specimens are provided to the investigator(s) without identifiers, and the supplier has established policies to prevent the release of personal information
- The study has been reviewed and approved by an IRB.

For more information see FDA [“Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable.”](#)

25.3.10. Applicable Regulations/Guidance

- FDA “Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable”(04/25/06);
- National Bioethics Advisory Commission “Research Involving Human Biological Materials: Ethical Issues and Policy Guidance” (08/99);
- NIH “Research Repositories, Databases, and the HIPAA Privacy Rule” (07/02/04); OHRP
- “Guidance on Research Using Coded Private Information or Specimens” (10/16/08);
- OHRP “Guidance on the Genetic Information Nondiscrimination Act: Implications for Investigators and Institutional Review Boards” (03/24/09);
- OHRP “Issues to Consider in the Research Use of Stored Data or Tissues”(11/07/97);
- “Report of the Public Responsibility in Medicine and Research (PRIM&R) Human Tissue/Specimen Banking Working Group”(03/07);
- The Secretary’s Advisory Committee on Human Research Protections (SACHRP)“FAQs ,Terms, and Recommendations on Informed Consent and Research Use of Biospecimens” (07/20/11)

25.4 Certificate of Confidentiality (CoC)

Certificates of Confidentiality are issued by the National Institutes of Health (NIH) or the Food and Drug Administration (FDA) to protect identifiable research information from forced disclosure. Researchers will need to apply for a CoC for non-federally funded research. Research being conducted under an IND or IDE should submit an application to the FDA for the CoC. A study funded in whole or in part by the NIH is automatically covered by a certificate of confidentiality and involves identifiable, sensitive information.

The application for a study that is not funded by the NIH or being conducted under an IND or IDE should be submitted to the NIH. The following are examples of research that is automatically covered by a CoC:

- Biomedical, behavioral, clinical or other research, including exempt research, except where the information obtained is recorded in such a manner that human subjects cannot be identified or the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects.
- The collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the

biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual.

- The generation of individual level, human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained.
- Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

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A CoC will allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. A CoC does not protect against voluntary disclosures by the investigator, but those disclosures must be specified in the informed consent form. An investigator may not use the CoC to withhold data if the participant consents in writing to the disclosure.

If a study has a CoC researchers:

- May not disclose or provide, in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- May not disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research.
- May disclose information only when:
 - Required by federal, state, or local laws (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to state and local health departments), excluding instances of disclosure in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding.
 - Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual.
 - Made with the consent of the individual to whom the information, document, or biospecimen pertains; or

- Made for the purposes of other scientific research that is in compliance with applicable federal regulations governing the protection of human subjects in research.
- Written materials require that when research is covered by a certificate of confidentiality, researchers must inform subjects (for example, in the consent document) of the protections and limitations of certificates of confidentiality:
 - For studies that were previously issued a Certificate, and subjects were notified of the protections provided by that Certificate, NIH does not expect subjects to be notified that the protections afforded by the Certificate have changed, although IRBs may determine whether it is appropriate to inform subjects.
 - If part of the study cohort was recruited prior to issuance of the Certificate, but are no longer actively participating in the study, NIH does not expect subjects consented prior to the change in authority, or prior to the issuance of a Certificate, to be notified that the protections afforded by the Certificate have changed, or that subjects who were previously consented to be re-contacted to be informed of the Certificate, although IRBs may determine whether it is appropriate to inform subjects.

25.4.1 Statutory Basis for Protection

Protection against compelled disclosure of identifying information about subjects of biomedical, behavioral, clinical, and other research is provided by the Public Health Service Act §301(d), 42 U.S.C. §241(d):

"The Secretary may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, including research on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals."

25.4.2 Usage

Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting investigators and institutions from being compelled to disclose information that would identify research subjects, CoCs help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to subjects.

Any investigator engaged in research in which sensitive information is gathered from human subjects (or any person who intends to engage in such research) may apply for a CoC. Research can be considered "sensitive" if it involves the collection of:

1. Research on HIV, AIDS, and STDs;
2. Information about sexual attitudes, preferences, practices;
3. Information about personal use of alcohol, drugs, or other addictive products;
4. Information about illegal conduct;
5. Information that could damage an individual's financial standing, employability, or reputation within the community;
6. Information in a subject's medical record that could lead to social stigmatization or discrimination; or
7. Information about a subject's psychological well-being or mental health.
8. Genetic studies, including those that collect and store biological samples for future use;
9. Research on behavioral interventions and epidemiologic studies.

This list is not exhaustive. Investigators contemplating research on a topic that might qualify as sensitive should contact the IRB Office for help in applying for a CoC.

Per NIH Grants Policy Statement the NIH considers research in which identifiable, sensitive information is collected or used, to include:

- Human subjects research as defined in the Federal Policy for the Protection of Human Subjects (45 CFR 46), including exempt research except for human subjects research that is determined to be exempt from all or some of the requirements of 45 CFR 46 if the information obtained is recorded in such a manner that human subjects cannot be identified or the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
- Research involving the collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual;
- Research that involves the generation of individual level, human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained as defined in the Federal Policy for the Protection of Human Subjects (45 CFR 46); or
- Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual, as defined in subsection 301(d) of the Public Health Service Act.

In the consent process and form, investigators should tell research subjects that a CoC is in effect. Subjects should be given a fair and clear explanation of the protection that it affords, including the limitations and exceptions noted above. Every research project that includes human research subjects should explain how identifiable information will be used or disclosed, regardless of whether or not a CoC is in effect.

25.4.3 Limitations

The protection offered by a Certificate of Confidentiality is not absolute. A CoC protects research subjects only from legally compelled disclosure of their identity. It does **not** restrict voluntary disclosures by subjects or investigators.

For example, a CoC does not prevent investigators from voluntarily disclosing to appropriate authorities such matters as child abuse, a subject's threatened violence to self or others, or from reporting a communicable disease. However, if investigators intend to make such disclosures, this should be clearly stated in the consent process and the form which research subjects are asked to sign.

In addition, a Certificate of Confidentiality does **not** authorize the person to whom it is issued to refuse to reveal the name or other identifying characteristics of a research subject if

1. The subject (or, if he or she is legally incompetent, his or her legal guardian) consents, in writing, to the disclosure of such information;
2. Authorized personnel of the Department of Health and Human Services (DHHS) request such information for audit or program evaluation, or for investigation of DHHS grantees or contractors and their employees; or
3. Release of such information is required by the federal Food, Drug, and Cosmetic Act or regulations implementing that Act.

25.4.4 Application Procedures

Any person engaged in research collecting sensitive information from human research subjects may apply for a Certificate of Confidentiality. For most research, CoC are obtained from NIH. If NIH funds the research project, the investigator may apply through the funding Institute. However, even if the research is not supported with NIH funding, the investigator may apply for a CoC through the NIH Institute or Center funding research in a scientific area similar to the project.

If the research is conducting a sensitive research project that is covered by the Agency for Healthcare Research and Quality (AHRQ) confidentiality statute (42 U.S.C. section 299a-1(c) entitled "Limitation on Use of Certain Information") or the Department of Justice (DoJ) confidentiality statute (42 USC section 3789g), then a CoC is not required.

If there is an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE), the sponsor can request a CoC from the FDA.

For more information, see the NIH Certificates of Confidentiality Kiosk (<http://grants.nih.gov/grants/policy/coc/index.htm>).

25.5 Mandatory Reporting

While any person may make a report if they have reasonable cause to believe that a child or elder was abused or neglected, Virginia law mandates that certain persons who suspect child or elder (60 or older) or incapacitated adult abuse or neglect report this to the Department of Social Services in the locality in which the child or elder/incapacitated adult lives or where the alleged abuse has occurred. Those designated by law as “mandated reporters” of child abuse or neglect include any person employed by a public or private institution of higher education, any person licensed, certified or registered by Virginia’s health regulatory boards, any professional staff person employed by the Medical Center or another hospital, and certified emergency medical services personnel.

Those designated by law as mandated reporters of elder/incapacitated abuse or neglect include any person licensed, certified or registered by Virginia’s health regulatory boards, any mental health services provider whether or not that individual is licensed or certified, certified emergency medical services personnel and any person working with adults in an administrative, supportive or direct care capacity. University of Virginia policy requires the solicitation of informed consent from all adult research subjects and, where appropriate, assent from children involved as research subjects, in addition to the permission of their parents. In situations where conditions of abuse or neglect might be revealed, mandated reporters should make themselves known as such to parents of children under age 18, to subjects who are children, and to subjects who are potential victims of abuse or neglect.

Children:

<http://law.lis.virginia.gov/vacode/title63.2/chapter15/section63.2-1509/>

<http://law.lis.virginia.gov/vacode/title63.2/chapter16/section63.2-1606/>

<http://law.lis.virginia.gov/vacode/title63.2/chapter16/section63.2-1603/>

The UVA Medical Center policy on abuse and neglect reporting may be found at:

<http://www.healthsystem.virginia.edu/docs/manuals/policies/mc/A70A3C0F-110A-2E68-14CB7CA516FAE39D/A70A4064-110A-2E68-14F9B61BA2D022C2/abuse-neglect-or-exploitation-of-patients>

Investigators should consult these sources to determine if potential subjects should be advised of mandatory reporting requirements during the informed consent process.

25.6 University of Virginia Students and Employees as Subjects

When University of Virginia students and/or employees are being recruited as potential subjects, investigators must ensure that there are additional safeguards for these subjects. The voluntary nature of their participation must be primary and without undue influence on their decision. Investigators must emphasize to subjects that neither their academic status or grades, or their employment, will be affected by their participation decision.

To minimize coercion, investigators should avoid enrolling, whenever possible, students currently enrolled in a course that they teach, students or employees that they supervise in procedures which are neither therapeutic nor diagnostic. In these latter situations, investigators should solicit subjects through means such as bulletin board notices, flyers, advertisements in newspapers, and announcements in classes or laboratories other than their own. When entering a classroom to recruit students and conduct research, e.g., administer a survey, investigators must do so at the end of the class period to allow non-participating students the option of leaving the classroom, thereby alleviating pressure to participate.

The University of Virginia allows for the creation of participant pools. Participant pools are a convenient way for researchers to access individuals (generally students) who are ready to participate in research. Student participant are generally organized around a particular discipline and help to facilitate students' access to research as part of their educational experience. It is acceptable to offer course credit for participating, but researchers are required to offer other opportunities to earn equivalent course credit. Researchers accessing students through a participant pools should offer educational insight to the student participating in their research.

25.7 Student Research

25.7.1 Human Subject Research and Course Projects

Learning how to conduct ethical human subject research is an important part of a student's educational experience. Research activities that are designed as part of a course requirement for purposes of learning experience only and are **not** "designed to develop or contribute to generalizable knowledge" **may** not require IRB review and approval if all of the following conditions are true:

- Results of the research are viewed only by the course instructor for teaching purposes and discussed within the classroom for teaching and learning purposes.
- Results of the research are not made public through presentation (outside of the classroom) and are not published in paper or electronic format (e.g., cannot be made available on the internet, cannot be published in a journal, etc.).
- Research procedures are no more than minimal risk.
- Vulnerable populations are not targeted (e.g., children under age 18, prisoners, persons who are cognitively impaired, etc.).

- Data collected are recorded in such a manner that the subjects are not identifiable (images in videotapes and photographs and voices on audiotape are identifiable).
- When appropriate, an informed consent process is in place.

25.7.1.1 Responsibility of the Course Instructor

The course instructor is responsible for communicating to the students the ethics of human subject research, for ensuring the protection of human subjects (including a process is in place for obtaining voluntary informed consent from research subjects when appropriate), and for monitoring the students' progress.

When designing a project, students should be instructed on the ethical conduct of research and on the preparation of the IRB application when such is required. In particular, instructors and students should:

- Understand the elements of informed consent;
- Develop appropriate consent documents or processes;
- Plan appropriate strategies for recruiting subjects;
- Identify and minimize potential risks to subjects;
- Assess the risk-benefit ratio for the project;
- Establish and maintain strict guidelines for protecting privacy and confidentiality, and
- Allow sufficient time for IRB review (if necessary) and completion of the project.

In making a determination of whether or not a class research project requires IRB review, the instructor is encouraged to contact the IRB office for assistance.

25.7.1.2 Individual Research Projects Conducted by Students

Independent study projects, senior theses, undergraduate research projects, Masters and advanced degree research, and similar exercises must be independently submitted for IRB review. It is important to keep in mind that any human subject research activity that will ultimately contribute to part or all of a thesis, dissertation, or other type of publication or presentation must go through the IRB review process prior to enrolling subjects and collecting data. IRB review/approval cannot occur after a study has begun.

Students and advisors should contact the IRB Office with any questions.

25.7.2 Independent Study, Theses and Dissertations

These research activities are considered to meet the federal definition of human subject research and must be independently submitted to the IRB by the student-investigator. However, when students conduct research as part of a course of study, a faculty member ultimately is responsible for the protection of the subjects, even if the student is the primary investigator and actually directs the project. The faculty adviser assumes the responsibility for

students engaged in independent research, and instructors are responsible for research that is conducted as part of a course. Students may serve as the principal investigator for social, behavioral or education research as long as they are able to secure a faculty advisor with expertise in their area of study.

25.8 Oral History

A decision whether oral history or other activities solely consisting of open ended qualitative type interviews are subject to the policies and regulations outlined in an institution's FWA and DHHS regulations for the protection of human research subjects (45 CFR 46) is based on the prospective intent of the investigator and the definition of "research" under DHHS regulations at 45 CFR 46.102(d): "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

Specifically, for the purposes of this policy, the evaluation of such activities hinges upon whether:

The activity involves a prospective research plan that incorporates data collection, including qualitative data, and data analysis to answer a research question; and

The activity is designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.

In order to be subject to the University of Virginia human research protections policies, the activity must meet both of the above standards. This determination will be made according to the procedures described in Section 5 above.

General principles for evaluating Oral History activities:

1. Oral history activities, such as open ended interviews, that ONLY document a specific historical event or the experiences of individuals without intent to draw conclusions or generalize findings do not constitute "research" as defined by DHHS regulations 45 CFR 46.

Example: An oral history video recording of interviews with holocaust survivors is created for viewing in the Holocaust Museum. The creation of the video tape does not intend to draw conclusions, inform policy, or generalize findings. The sole purpose is to create a historical record of specific personal events and experiences related to the Holocaust and provide a venue for Holocaust survivors to tell their stories.

2. Systematic investigations involving open-ended interviews that are designed to develop or contribute to generalizable knowledge (e.g., designed to draw conclusions, inform policy, or generalize findings) would constitute "research" as defined by DHHS regulations at 45 CFR 46.

Example: An open ended interview of surviving Gulf War veterans to document their experiences and to draw conclusions about their experiences, inform policy, or generalize findings.

Investigators are advised to consult with the IRB Office regarding whether their oral history project requires IRB review.

25.9 Genetic Studies

Genetic research studies may create special risks to human subjects and their relatives. These involve medical, psychosocial, legal and economic risks, such as the possible loss of privacy, insurability, and employability, change in immigration status and limits on education options, and may create a social stigma. Knowledge of one's genetic make-up may also affect one's knowledge of the disease risk status of family members.

In studies involving genetic testing, several questions need to be addressed, including:

1. Will test results be given?
2. Will disease risk be quantified, including the limits on certainty of the testing?
3. Will a change in a family relationship be disclosed, such as mistaken paternity?
4. Does the subject or family member have the option not to know the results? How will this decision be recorded?
5. Could other clinically relevant information be uncovered by the study? How will disclosure of this added information occur?
6. Do any practical limitations exist on the subject's right to withdraw from the research, withdraw data, and/or withdraw DNA?
7. Is the subject permitted to participate in the study while refusing to have genetic testing (such as in a treatment study with a genetic testing component)?

For DNA banking studies, several questions need to be addressed, including:

1. Will DNA be stored or shared? If shared, will the subject's identity be known by the new recipient investigator?
2. Will the subject be contacted in the future by the investigator to obtain updated clinical information?
3. How can the subject opt out of any distribution or subsequent use of his/her genetic material?

25.10 Case Reports Requiring IRB Review

In general, an anecdotal report on up to three patients seen in one's own practice and a comparison of these patients to existing reports in the literature is not research and does not require IRB approval. Going beyond one's own practice to seek out and report cases seen by other clinicians creates the appearance of a systematic investigation with the intent to contribute to generalizable knowledge and therefore is considered research and would require IRB approval.

25.10.1 Definitions

Single Case Report. The external reporting (e.g., publication, poster or oral presentation) of an interesting clinical situation or medical condition of a single patient. Case reports normally contain detailed information about an individual patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The patient information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.

Case Series. The external reporting (e.g., publication, poster or oral presentation) of an interesting clinical situation or medical condition in a series of up to three patients (i.e., more than one patient). Case series usually contain detailed information about each patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.

25.11 Research supported by the Department of Defense (DoD)

Research supported by the Department of Defense (DoD) is reviewed and conducted in compliance with part 219 of title 32 CFR, part 980 of title 10 USC, applicable parts of title 21 CFR (50, 56, 312, 600, 812), DoD Instruction 3216.02, DoD Directive 3210.07, and applicable additional requirements from respective DoD component(s).

DoD Components refers collectively to the organizational entities within the DoD that are subject to the human subjects protections laid out in Department of Defense Directive

A. Application and Scope

The following additional requirements apply to all biomedical and social/behavioral research involving human research participants conducted under the jurisdiction of University of Virginia when it:

- Conducts, reviews, approves, oversees, supports manages otherwise is contractually subject to regulation by the DoD; and/or
- Human subject research performed under the jurisdiction of University of Virginia using DoD property, facilities, or assets.

In most cases, protocols covered by these requirements also will have review, approval and oversight by the DoD Human Research Protections Program.

University of Virginia assures that DoD supported research complies with all relevant DoD human subjects protection requirements, including but not limited to:

- The Belmont Report

- Title 32 Code of Federal Regulations Part 219 (32 CFR 219), Department of Defense Regulations, “Protection of Human Subjects” (DoD adoption of the “Common Rule”)
- Title 45 Code of Federal Regulations Part 46, (45 CFR 46) Department of Health and Human Services Regulations, “Protection of Human Subjects,” Subparts B, C, and D as made applicable by DoD Directive (DoDD) 3216.02
- Title 21 Code of Federal Regulations 50, 56, 312, and 812, Food and Drug Administration (FDA) Regulations
- DoDD 3216.02, “Protection of Human Subjects and Adherence to Ethical Standards in DoD-supported Research”
- Title 10 United States Code Section 980 (10 USC 980), “Limitation on Use of Humans as Experimental Subjects”
- DoDD 3210.7, “Research Integrity and Misconduct”
- DoDD 6200.2, “Use of Investigational New Drugs in Force Health Protection”

B. Key Additional Requirements Not Covered by Title 45 CFR 46, Subparts B, C and D; 21 CFR 50, 56, 312, and 812

1. *Minimal Risk – [DoDI 316.02, enclosure 3, para 6b]*

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

2. *Undue Influence – [DoDD 3216.2, enclosure 3, para 7e1]*

Service members shall follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty and for approving off-duty employment or activities. Superiors (e.g., military and civilian supervisors, unit officers, and noncommissioned officers (NCOs)) are prohibited from influencing the decisions of their subordinates (e.g., junior enlisted personnel and equivalent civilians) regarding participation as subjects in research involving human subjects. Unit officers and senior NCOs in the chain of command shall not be present at the time of research subject solicitation and consent during any research recruitment sessions in which members of units under their command are afforded the opportunity to participate as research subjects. When applicable, officers and NCOs so excluded shall be afforded the opportunity to participate as research subjects in a separate recruitment session. During recruitment briefings to a unit where a percentage of the unit is being recruited to participate as a group, an ombudsman not connected in any way with the proposed research or the unit shall be present to monitor that the voluntary nature of individual participants is adequately stressed and that the information provided about the research is adequate and accurate.

3. Education and Training – [DoDD 3216.2, enclosure 3, para 5]

For initial and continuing research ethics education for all personnel who conduct, review, approve, oversee, support, or manage human participant research is required. The DoD component may evaluate the education policies to ensure the personnel are qualified to perform the research, based on the complexity and risk of the research.

4. Appointment of a Research Monitor – [DoDI 3216.02, enclosure 3, para 8]

- The IRB considers the appointment of a research monitor:
 - Required for research involving greater than minimal risk, although the IRB or organizational official can require this for a portion of the research or studies involving no more than minimal risk if appropriate.
 - The research monitor is appointed by name and shall be independent of the team conducting the research.
 - There may be more than one research monitor (e.g. if different skills or experience are needed).
 - The monitor may be an ombudsman or a member of the data safety monitoring board.
 - The IRB staff shall communicate with research monitors to confirm their duties, authorities, and responsibilities.
 - The duties of the research monitor are determined on the basis of specific risks or concerns about the research.
 - May perform oversight functions (e.g. observe recruitment, enrollment procedures, and the consent process, oversee study interventions and interactions, review monitoring plans and unanticipated problems involving risks to participants or others, oversee data matching, data collection and analysis).
 - May discuss the research protocol with researchers, interview human subjects, and consult with others outside of the study.
 - Report observations and findings to the IRB or a designated official.
- The research monitor has the authority to:
 - Stop a research study in progress.
 - Remove individuals from study.
 - Take any steps to protect the safety and well-being of participants until the IRB can assess.

5. Additional protections for pregnant women, prisoners, and children (Subparts B, C and D) of 45 CFR 46) – [DoDI 3216.02, enclosure 3 para 7]

- Research involving pregnant women, prisoners, and children are subject to the DHHS Subparts B, C. and D.
 - For purposes of applying Subpart B, the phrase “biomedical knowledge” shall be replaced with “generalizable knowledge.”

- 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.
- Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.
- 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 a detainee as a human participants is prohibited.
- Research involving prisoners cannot be reviewed by the expedited procedure.
- When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum.
- In addition to allowable categories of research on prisoners in Subpart C, epidemiological research is also allowable when:
 - The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.
 - The research presents no more than minimal risk
 - The research presents no more than an inconvenience to the participant.
- When a prisoner becomes a participant, if the researcher asserts to the IRB that it is in the best interest of the prisoner-participant to continue to participate in the research while a prisoner, the IRB Chair may determine that the prisoner-participant may continue to participate until the convened IRB can review this request to approve a change in the research protocol and until the organizational official and DoD Component office review the IRB's approval to change the research protocol. Otherwise, the IRB Chair shall require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened IRB can review this request to approve a change in the research protocol. The convened IRB, upon receipt of notification that a previously enrolled human participant has become a prisoner, shall promptly re-review the research protocol to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert having the expertise of a prisoner representative if the IRB reviewing the research protocol does not have a prisoner representative. If the prisoner-participant can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-participant's confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human participants from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-participant to continue to participate in the research. This approval is limited to the individual prisoner-participant and does not allow recruitment of prisoners as participants.

6. *Limitation of Waivers and Exceptions from Informed Consent - [DoDI 3216.02, enclosure 3 para 13; 10 U.S.C. 980]*

The requirements of title 10 United States Code 980 which are applicable to DoD sponsored research must be considered. 10 USC 980 requires that “Funds appropriated to the Department of Defense may not be used for research involving a human being as an Experimental Subject unless 1) the informed consent of the subject is obtained in advance; or 2) in the case of research intended to be beneficial to the subject, the informed consent may be obtained from a legal representative of the subject.

The definition of experimental subject is found in DODI 3216.02 and has a much narrower definition than human subject under 45CFR46. Research with experimental subjects must involve an intervention or interaction where the primary purpose of the research is to collect data regarding the effects of the intervention or interaction.

An individual not legally competent to provide informed consent (e.g. , incapacitated individuals, cognitively impaired, minors) may not be enrolled as an experimental subject in a DOD –supported experiment unless participation in the research is intended to benefit each subject enrolled in the study, to include subjects enrolled in study placebo arms. Studies designed in a manner that permits all subjects to potentially benefit directly from medical treatment or enhanced surveillance beyond the standard of care can meet the 10 USC 980 requirements.

10 USC 980 is only applicable to certain intervention studies. It does not apply to retrospective studies, observational studies, blood draws, and tissue collections.

If the research participant meets the definition of “experimental subject,” policies and procedure prohibit a waiver of the consent process unless a waiver is obtained from the Assistant Secretary of Defense for Research and Engineering. The Assistant Secretary of Defense for Research and Engineering may waive the requirements for consent when all of the following are met:

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

For classified research, waivers of consent are prohibited.

7. *Limitations on Compensation for U.S. Military Personnel - [Dual Compensation Act and 24 U.S.C. 30]*

The Dual Compensation Act prohibits an individual from receiving pay from more than one position for more than an aggregate of 40 hours of work in one calendar week. This prohibition applies to employees paid from either appropriated or non-appropriated funds, or a

combination thereof, and includes temporary, part-time and intermittent appointments. This law if not applicable to enlisted off-duty military personnel in relation to their military duty.

When research involves U.S. military personnel, limitations on dual compensation include:

- Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to \$50 for each blood draw.
- Non-Federal persons may be compensated for research participation other than blood draws in a reasonable amount, as approved by the IRB according to local prevailing rates and the nature of the research.
- Prohibit an individual from receiving pay of compensation for research during duty hours.
- U.S. military personnel may be compensated for research if the participant is involved in the research when not on duty.

8. *Requirement for Reporting - DoDI 3216.02, enclosure 3 para 4(b)(4)*

The Institution shall promptly (no longer than within 30 days) notify the HRPO of the following: when significant changes to the research protocol are approved by the IRB, the results of the IRB continuing review, if the IRB used to review and approve the research changes to a different IRB, when the institution is notified by any Federal department or agency or national organization that any part of its HRPP is under investigation for cause involving a DoD-supported research protocol, and all UPIRTSOs, suspensions, terminations, and serious or continuing noncompliance regarding DoD-supported research involving human subjects.

9. *Recordkeeping Requirements - [DoDD 3216.2, para. 5.3.2; SECNAVINST 3900.39D, para. 8c(18)]*

Recordkeeping requirements for DOD-supported research with human subjects are longer than the Common Rule's requirement. DOD may require submitting records to DOD for archiving.

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

10. *Addressing and Reporting Allegations of Non-Compliance with Human Research Protections - [DoDD 3216.2, para. 4.10; SECNAVINST 3900.39D, para. 8d(2) and 6k]*

Report the initiation of all investigations and report results regardless of the findings to the Navy Secretary General and appropriate sponsors.

11. *Addressing and Reporting Allegations of Research Misconduct - [DoDD 3216.2, para. 4.8; DODD 3210.7; SECNAVINST 3900.39D, 8d(2) para. 6l]*

All findings of serious research misconduct under this section shall be reported to the Director, Defense Research and Engineering.

12. Provisions for Research with Human Subjects using Investigational Test Articles (Drugs, Device and Biologics) - [DoDD 3216.2, para 4.9; DoDD 6200.2; SECNAVINST 3900.39D, para. 6h]

Principal investigators may not be sponsors for INDs and IDEs.

13. Prohibition of Research with Prisoners of War (POW) and Detainees - [DoDD 3216.2, para 4.4.2; SECNAVINST 3900.39D, para. 6a(8)]

Research involving any person captured, detained, held or otherwise under the control of DoD personnel (military and civilian, or contractor employee) is prohibited.

14. Classified research[DoDI 3216.02, enclosure 3 para 13]

The involvement of classified information may be limited to information needed for IRB approval and oversight of the research; information needed to inform the human subjects during the consent process; and information provided by the human subjects during the course of the research. Secretary of Defense approval is required for all classified non-exempt research involving human subjects.

Informed consent procedures shall include:

- (1) Identification of the Department of Defense as the supporting institution of the research, unless the research involves no more than minimal risk. The Secretary of Defense may grant an exception to this requirement on the grounds that providing this information could compromise intelligence sources or methods.
- (2) A statement that the research involving human subjects is classified and an explanation of the impact of the classification.

The IRB shall determine whether potential human subjects need access to classified information to make a valid, informed consent decision.

IRB review shall be conducted using a full board review. Use of an expedited review procedure is prohibited.

15. Additional Requirements for DoD Sponsored Research

- a) New research and substantive scientific amendments to approved research shall undergo scientific review and the review is considered by the IRB. The IRB may rely on outside experts to provide an evaluation of scientific merit.
- b) When conducting research with international populations, additional safeguards for research conducted with international populations include: The Organization or

Researcher has permission to conduct research in that country by certification or local ethics review and the Researcher follows all local laws, regulations, customs, and practices.

- c) Disclosure regarding the provisions for research-related injury follow the requirements of the DoD component.
- d) Surveys performed on Department of Defense personnel must be submitted, reviewed, and approved by the Department of Defense after the research protocol is reviewed and approved by the IRB.
- e) When conducting multi-site research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.
- f) The following shall be promptly (no longer than within 30 days) reported to the DoD human research protection officer:
 - a. When significant changes to the research protocol are approved by the IRB.
 - b. The results of the IRB continuing review.
 - c. Change of reviewing IRB.
 - d. When the organization is notified by any Federal department, agency or national organization that any part of the HRPP is under investigation for cause involving a DoD-supported research protocol.
- g) If consent is to be obtained from the research participant's LAR, the research must intend to benefit the individual participant. The determination that research is intended to be beneficial to the individual research participant must be made by the IRB.
- h) Civilian researchers attempting to access military volunteers should seek collaboration with a military researcher familiar with service-specific requirements.

C. Responsibilities

It is the responsibility of the principal investigator to ensure compliance with all additional Department of Defense (DoD) requirements for human subject protection. It also is the responsibility of the IRB to ensure that all additional requirements by Department of Defense components for human subject protection have been met before IRB approval of the research project.

25.12 Research Supported by the Department of Justice (DOJ)

To ensure that human subjects are adequately protected from unreasonable risks and properly informed of the potential harms and benefits from their participation in research, the National Institute of Justice (NIJ) and recipients of its funds are required to comply with 28 CFR Part 46 (Protection of Human Subjects) or the "Common Rule."

All projects funded under NIJ are required to submit a NIJ Privacy Certificate. Submission of a Privacy Certificate as part of an IRB application is required regardless of whether the project involves the collection of identifiable data. In cases where no personally identifiable information will be collected, the Privacy Certificate should contain a statement to this effect and a brief project description. The Privacy Certificate assures that the applicant

understands his responsibilities to protect the confidentiality of research and statistical information and has developed specific procedures to ensure that this information is only used or revealed in accordance with the requirements of 42 USC §3789g and 28 CFR Part 22. The Privacy Certificate is signed by the Principal Investigator(s), submitted with the IRB application, and is then signed by the IO upon successful completion of the IRB processes. The principal investigator is responsible for submitting the completed Privacy Certificate to NIJ. Privacy Certificate instructions and guidelines can be found at the NIJ website.

All researchers and research staff are required to sign employee confidentiality statements, which are maintained by the responsible researcher.

It is the responsibility of the principal investigator to ensure compliance with any additional NIJ requirements for human subject protection. It also is the responsibility of the IRB to ensure that additional requirements for human subject protection have been met prior to IRB approval of the research project.

For research conducted within the Bureau of Prisons: Implementation of Bureau programmatic or operational initiatives made through pilot projects are not considered to be research.

Additionally, for all research conducted within the Bureau of Prisons, UVA, the IRBs, and researchers and research staff must follow the requirements of 28 CFR 512, including:

- The project must not involve medical experimentation, cosmetic research, or pharmaceutical testing.
- The research design must be compatible with both the operation of prison facilities and protection of human subjects. The researcher must observe the rules of the institution or office in which the research is conducted.
- Any researcher who is a non-employee of the Bureau must sign a statement in which the researcher agrees to adhere to the provisions of 28 CFR 512.
- All research proposals will be reviewed by the Bureau Research Review Board.

Further considerations include:

- A non-employee of the Bureau may receive records in a form not individually identifiable when advance adequate written assurance that the record will be used solely as a statistical research or reporting record is provided to the agency.
- Except as noted in the consent statement to the subject, the researcher must not provide research information that identifies a subject to any person without that subject's prior written consent to release the information. For example, research information identifiable to a particular individual cannot be admitted as evidence or used for any purpose in any action, suit, or other judicial, administrative, or legislative proceeding without the written consent of the individual to whom the data pertain.

- Except for computerized data records maintained at an official DoJ site, records that contain non-disclosable information directly traceable to a specific person may not be stored in, or introduced into, an electronic retrieval system.
- If the researcher is conducting a study of special interest to the Office of Research and Evaluation (ORE) but the study is not a joint project involving ORE, the researcher may be asked to provide ORE with the computerized research data, not identifiable to individual subjects, accompanied by detailed documentation. These arrangements must be negotiated prior to the beginning of the data collection phase of the project.

The research protocol submitted to the IRB must address the following:

- Research conducted within the Bureau of Prisons must have an adequate research design and contribute to the advancement of knowledge about corrections.
- The selection of subjects within any one organization must be equitable
- Incentives may not be offered to help persuade inmate subjects to participate; however soft drinks and snacks to be consumed at the test setting may be offered.
- Reasonable accommodations such as nominal monetary recompense for time and effort may be offered to non-confined research subjects who are both no longer in Bureau of Prisons custody and participating in authorized research being conducted by Bureau employees or contractors.
- The researcher must have academic preparation or experience in the area of study of the proposed research.
- The researcher must assume responsibility for actions of any person engaged to participate in the research project as an associate, research coordinator, sub investigator or subcontractor to the researcher.
- The researcher must include the following in the application to the IRB:
 - A summary statement, which includes:
 - Names and current affiliations of the researchers
 - Title , purpose and location of the study
 - Methods to be employed
 - Anticipated results
 - Duration of the study
 - Number of subjects (staff or inmates) required and amount of time required from each
 - Indication of risk or discomfort involved as a result of participation
 - A comprehensive statement, which includes:
 - Review of related literature
 - Detailed description of the research method
 - Significance of anticipated results and their contribution to the advancement of knowledge
 - Specific resources required from the Bureau of Prisons

- Description of all possible risks, discomforts, and benefits to individual subjects or a class of subjects, and a discussion of the likelihood that the risks and discomforts will actually occur.
- Description of steps taken to minimize any risks
- Description of any anticipated effects of the research study on organizational programs and operations
- Relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules.
- A statement regarding assurances and certification required by 28CFR46, if applicable.
- The following consent elements are required:
 - For National Institute of Justice (NIJ)-funded research the consent document must disclose:
 - The name(s) of the funding agency(ies).
 - For research conducted within the Bureau of Prisons required elements of disclosure include:
 - The identity of the researchers.
 - Anticipated uses of the results of the research.
 - The extent to which confidentiality of records identifying the subject will be maintained. For studies sponsored by NIJ, the subject should be informed that private, identifiable information will be kept confidential and will only be used for research and statistical purposes. If, due to sample size or some unique feature, the identity of the individual cannot be maintained, the subjects need to be explicitly notified. If the researcher intends to disclose any information, the subject needs to be explicitly informed what information would be disclosed, under what circumstances, and to whom. The subject must be informed of any risks that might result from this disclosure and must explicitly provide written consent prior to participating in the research.
 - A statement that participation is completely voluntary and that the subject may withdraw consent and end participation in the project at any time without penalty or prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable).
 - A statement regarding the confidentiality of the research information and exceptions to any guarantees of confidentiality required by federal or state law. For example, a researcher may not guarantee confidentiality when the subject indicates intent to commit future criminal conduct or harm himself or herself or someone else, or, if the subject is an inmate, indicates intent to leave the facility without authorization.

- A statement that participation in the research project will have no effect on the inmate subject's release date or parole eligibility.

For National Institute of Justice-funded research, a copy of all data must be de-identified and sent to the National Archive of Criminal Justice Data, including copies of the informed consent document, data collection instruments, surveys, or other relevant research materials.

- At least once a year, the researcher shall provide the chief, Office of Research and Evaluation, with a report on the progress of the research.
- At least 12 working days before any report of findings is to be released, the researcher shall distribute one copy of the report to each of the following: the chairperson of the Bureau Research Review Board, the regional director, and the warden of each institution that provided data or assistance. The researcher shall include an abstract in the report of findings.
- In any publication of results, the researcher shall acknowledge the Bureau's participation in the research project.
- The researcher shall expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
- Prior to submitting for publication the results of a research project conducted under this subpart, the researcher shall provide two copies of the material, for informational purposes only, to the Chief, Office of Research and Evaluation, Central Office, Bureau of Prisons.

25.13 Department of Education: The Protection of Pupil Rights Amendment (PPRA) and the Family Educational Rights and Privacy Act (FERPA)

Research funded through the Department of Education must comply with additional regulatory requirements under 34 CFR 98.3, 34 CFR 98.4, 34 CFR 99, 34 CFR 356.3

25.13.1 Protection of Pupil Rights Amendment (PPRA)

The Protection of Pupil Rights Amendment (PPRA) (20 U.S.C. § 1232h; 34 CFR Part 98) applies to programs that receive funding from the U.S. Department of Education (ED). PPRA is intended to protect the rights of parents and students.

No student shall be required, as part of any research project, to submit without prior consent (parental permission and assent) to surveys, psychiatric examination, testing, or treatment, or psychological examination, testing, or treatment, in which the primary purpose is to reveal information concerning one or more of the following:

- Political affiliations
- Mental and psychological problems potentially embarrassing to the student or his or her family
- Sex behaviors and attitudes
- Illegal, anti-social, self-incriminating and demeaning behavior

- Critical appraisals of other individuals with whom the student has close family relationships
- Legally recognized privileged & analogous relationships, such as those of lawyers, physicians & ministers
- Religious practices, affiliations, or beliefs of the student or student's parent
- Income, other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under a program

Prior consent means:

- Prior consent of the student, if the student is an adult (age 18 or older) or emancipated through a court order
- Prior written consent (permission) of the parent or legal guardian, if the student is an un-emancipated minor.

The University of Virginia IRB does not consider waivers under PPRA.

PPRA also requires parental notification and the opportunity to opt their child out of any non-emergency, invasive physical exam or screening required as a condition of attendance, administered by the school or its agent, and not necessary to protect the immediate health and safety of the student. There is an exception for State mandated exams.

For certain research not directly funded by the ED and conducted in a school that receives funding from the ED: The IRB must verify compliance with the ED regulations that schools are required to develop and adopt policies in conjunction with parents regarding the following:

- The right of a parent of a student to inspect, upon the request of the parent, a survey created by a third party before the survey is administered or distributed by a school to a student including any applicable procedures for granting a request by a parent for reasonable access to such survey within a reasonable period of time after the request is received.
- Arrangements to protect student privacy that are provided by the agency in the event of the administration or distribution of a survey to a student containing one or more of the topics covered under PPRA.
- The right of a parent of a student to inspect, upon the request of the parent, any instructional material used as part of the educational curriculum for the student.
- Any applicable procedures for granting a request by a parent for reasonable access to instructional material received.
- The administration of physical examinations or screenings that the school or agency may administer to a student.
- The collection, disclosure, or use of personal information collected from students for the purpose of marketing or for selling that information (or otherwise providing that information to others for that purpose), including arrangements to protect student privacy that are provided by the agency in the event of such collection, disclosure, or use.
- The right of a parent of a student to inspect, upon the request of the parent, any instrument used in the collection of personal information before the instrument is administered or distributed to a student.
- Any applicable procedures for granting a request by a parent for reasonable access to such instrument within a reasonable period of time after the request is received.

PPRA also requires parental notification and the opportunity to opt their child out of any non-emergency, invasive physical exam or screening required as a condition of attendance, administered by the school or its agent, and not necessary to protect the immediate health and safety of the student. There is an exception for State mandated exams.

25.13.2 Family Education Rights and Privacy Act (FERPA)

The Family Educational Rights and Privacy Act (FERPA) is a Federal law that protects the privacy of student education records. The law applies to all schools that receive funds under an applicable program of the U.S. Department of Education.

FERPA gives parents certain rights with respect to their children's education records. These rights transfer to the student when he or she reaches the age of 18 or attends a school beyond the high school level. Students to whom the rights have transferred are "eligible students."

25.13.3 Conditions for Which Student Records Can Be Disclosed without Consent for Research Purposes

Schools may disclose, without consent, "directory" information such as a student's name, address, telephone number, date and place of birth, honors and awards, and dates of attendance. However, schools must tell parents and eligible students about directory information and allow parents and eligible students a reasonable amount of time to request that the school not disclose directory information about them. Schools must notify parents and eligible students annually of their rights under FERPA. The actual means of notification (special letter, inclusion in a PTA bulletin, student handbook, or newspaper article) is left to the discretion of each school.

For research purposes, FERPA allows schools to disclose students' educational records, without consent, to the following parties or under the following conditions (34 CFR § 99.31),

- The Researcher will receive a completely de-identified data set from the educational institution. Personal identifiers include:
 - Student's name and other direct personal identifiers, such as the student's social security number or student number.
 - Indirect identifiers, such as the name of the student's parent or other family members; the student's or family's address, and personal characteristics or other information that would make the student's identity easily traceable; date and place of birth and mother's maiden name.
 - Biometric records, including one or more measurable biological or behavioral characteristics that can be used for automated recognition of an individual, including fingerprints, retina and iris patterns, voiceprints, DNA sequence, facial characteristics, and handwriting.
 - Other information that, alone or in combination, is linked or linkable to a specific student that would allow a reasonable person in the school community, who does not have personal knowledge of the relevant circumstances, to identify the student with reasonable certainty.

- An educational agency or institution may disclose personally identifiable information from an education record of a student without consent if the disclosure is to organizations conducting studies for, or on behalf of, educational agencies or institutions to:
 - Develop, validate, or administer predictive tests.
 - Administer student aid programs.
 - Improve instruction.
- A school district or postsecondary institution that uses this exception is required to enter into a written agreement with the organization or researcher conducting the research that specifies:
 - The determination of the exception.
 - The purpose, scope, and duration of the study.
 - The information to be disclosed.
 - That information from education records may only be used to meet the purposes of the study stated in the written agreement and must contain the current requirements in 34 CFR 99.31(a)(6) on re-disclosure and destruction of information.
 - That the study will be conducted in a manner that does not permit personal identification of parents and students by anyone other than representatives of the organization with legitimate interests.
 - That the organization is required to destroy or return all personally identifiable information when no longer needed for the purposes of the study.
 - The time period during which the organization must either destroy or return the information.

25.13.4 Requests for Waivers of Consent

It is important that researchers apply FERPA and human subject protection regulations when accessing educational records. Generally FERPA and IRB requirements are met if a student or parent signs a consent form to participate in a study and authorizes release of his/her educational records for research purposes. In instances where a researcher requests to waive the informed consent process, the following conditions must be met:

25.13.4.1 Research on University of Virginia Student Records

- If records are being requested from the University of Virginia, the researcher must secure the appropriate approvals from the University Registrar, the Office of Institutional Research and Analytics, or Student Health. This permission must be attached be submitted with the IRB protocol application. The University Registrar or the Office of Institutional Research and Analytics will make the final determination if the study meets the FERPA criteria to release educational information without a signed consent form.

25.13.4.2 Research on Student Records at Institutions other than the University of Virginia

Where researchers are conducting a study on behalf of the school district or other educational institution or setting to improve instruction or to develop or validate a predictive test, the school district may provide FERPA protected records without consent under specific conditions and pursuant to a written agreement between the school district and the researcher. If researchers are proposing to

access student records at institutions other than the University of Virginia, utilizing a waiver of consent then the researchers should contact that institution and follow that institution's FERPA policy.

Researchers must provide the school district with a copy of their research proposal outlining all research procedures. Written permission must be secured by the researcher from the proper authority such as the District Superintendent or Head of School. This permission must be uploaded with the IRB protocol application.

Additional considerations include:

- In accordance with FERPA, an educational institution has the authority to determine what information may be accessed from an educational record. If an institution denies an investigator access to information in an educational record, the IRB cannot overrule the decision.
- According to the IRB federal regulations, for non-exempt studies, an IRB cannot waive informed consent or documentation of informed consent unless specific conditions are met. Consequently, researchers should include rationale for waiver requests in the IRB application even in circumstances where FERPA allows access without prior consent.
- FERPA and the Health Insurance Portability and Accountability Act (HIPAA) regulations provide conflicting requirements for medical records. In some situations FERPA is more restrictive than HIPAA for researchers. Researchers should contact each educational institution and follow that institution's applicable policies, whether FERPA and/or HIPAA policy when accessing student medical records.

25.13.5 Other Department of Education Requirements:

For research funded by the Department of Education, the researcher must allow access to instructional material used in a research or experimentation program including:

- Teachers' manuals, films, tapes, or other supplementary instructional material--which will be used in connection with any research or experimentation program or project must be available for inspection by the parents or guardians of the children engaged in such research.

25.13.6 Definitions:

Research or experimentation program or project means any program or project in any research that is designed to explore or develop new or unproven teaching methods or techniques.

Children are persons enrolled in research not above the elementary or secondary education level, who have not reached the age or majority as determined under state law.