



Human Research Protections
Program
Office of Research Integrity &
Compliance
West Virginia University

Standard Operating Procedures

August 2014

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 <p>Human Research Protections Program (HRPP)</p> <p>Office of Research Integrity & Compliance</p> <p>STANDARD OPERATING PROCEDURES</p>	<p>Section #: 1</p> <p>Title: Human Research Protections Program (HRPP)</p> <p>Date: December 10, 2010</p> <p>Page: Page 11 of 194</p>
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1 Human Research Protections Program (HRPP)

West Virginia University (WVU) 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 WVU. In the review and conduct of research, actions by WVU 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*** (often referred to as the *Belmont Report*). The actions of WVU will also conform to all applicable federal, state, and local laws and regulations. In order to fulfill this policy, WVU has established a Human Research Protections Program (HRPP) within the Office of Research Integrity and Compliance (ORIC).

1.1 Mission

The mission of the WVU HRPP is to:

- To safeguard and promote the health and welfare of human research subjects by ensuring that their rights, safety and well-being are protected;
- 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:

- Establish a formal process 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 Institutional Authority

The WVU Human Research Protection Program operates under the authority of the Organization policy “Human Research Protection Program” adopted on August 17, 2010. 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 ORIC.” The HRPP Policy and these operating procedures are made available to all ORIC investigators and research staff and are posted on the ORIC website (<http://oric.research.wvu.edu>).

WVU provides IRB review for human subjects research conducted at the **Louis A. Johnson Veterans Affairs Medical Center (LAJVAMC)** under a Memorandum of Understanding. Projects reviewed for the **LAJVAMC** receive the same IRB review as those conducted at WVU.

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 Department of Health and Human Services (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 Subjects Research – means any activity that meets the definition of “research” and involves “human subjects” as defined by either the Common Rule or FDA regulations.

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

Research. The Common Rule defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge.

For the purposes of this policy, a “**systematic investigation**” is an activity that involves a prospective study plan which 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.

Research 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 (21 CFR 50 and 56), human subject means an individual who is or becomes a participant in a clinical investigation (as defined below), 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/participant also includes any individual on whose tissue specimen an investigational device is used or tested.

Test Article. Test articles covered under the FDA regulations include:

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. <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 - In its broadest sense, a food additive is any substance added to food. Legally, the term refers to "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 characteristics of any food." This definition includes any substance used in the production, processing, treatment, packaging, transportation or storage of food.

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.

<http://www.fda.gov/Food/FoodIngredientsPackaging/ucm094211.htm#foodadd>

f. Foods, including dietary supplements that bear a nutrient content claim or a health claim

g. Infant formulas

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

Institutional Official (IO). The IO is responsible for ensuring that the HRPP at WVU has the resources and support necessary to comply with all federal regulations and guidelines that govern human subjects research. The IO is legally authorized to represent the institution, is the signatory official for all Assurances, and assumes the obligations of the institution's Assurance.

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

Engagement. WVU is considered *engaged* in a research project when the involvement of their employees or agents in that project includes any of the following:

- Intervention for research purposes with any human subjects of the research by performing invasive or noninvasive procedures.
- Intervention for research purposes with any human subject of the research by manipulating the environment.
- Interaction for research purposes with any human subject of the research.
- Obtaining the informed consent of human subjects for the research.
- Obtaining for research purposes identifiable private information or identifiable biological specimens from any source for the research. In general, obtaining identifiable private information or identifiable specimens includes, but is not limited to:
 - observing or recording private behavior;
 - using, studying, or analyzing for research purposes identifiable private information or identifiable specimens provided by another institution; and
 - using, studying, or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the investigators.

Agent. Agents include all individuals performing institutionally designated activities or exercising institutionally delegated authority or responsibility.

1.4 Ethical Principles

WVU is committed to conducting research with the highest regard for the welfare of human subjects. It 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 is ensured by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.

- 2) **Beneficence**, which is assured by ensuring that possible benefits are maximized and possible risks are minimized to all human subjects.
- 3) **Justice**, the equitable selection of subjects.

The WVU Human Research Protection Program (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.

1.5 Regulatory Compliance

The HRPP is responsible for ensuring compliance with federal regulations, state law and institutional policies. All human subjects research at WVU is conducted in accordance with the policy and regulations found in the Common Rule and 21 CFR 50 and 56. Where federal agencies have additional requirements, see the following guidance documents:

- Additional Department Of Defense (“DOD”) - Department Of The Navy (“DON”) Requirements--Human Subjects Protections
- Additional Department of Education Requirements--Human Subjects Protections
- Additional Department of Energy Requirements--Human Subjects Protections
- Additional Department of Justice Requirements--Human Subjects Protections
- Additional Environmental Protection Agency Requirements--Human Subjects Protections

The actions of WVU will also conform to all other applicable federal, state, and local laws and regulations.

WVU voluntarily applies the International Conference on Harmonization (“ICH”) Good Clinical Practices (“GCP”) Guidelines (sometimes referred to as “ICH-GCP” or “E6”) to certain types of human subjects research conducted under its HRPP. In general, WVU applies the ICH-GCP guidelines only to the extent that they are compatible with FDA and DHHS regulations. When a sponsor requires institutional ICH-GCP compliance, the IRB will conduct a review in accord with ICH-GCP requirements. See the document “International Conference on Harmonization (ICH) Good Clinical Practices (GCP), Applicability to Human Subjects Research” for guidance on the applicability of the ICH-GCP requirements.

To honor its commitment to the LAJVAMC, the University abides by the Department of Veterans Affairs policies for human research protection, including the regulations at 38 CFR 16, and the VHA Handbooks 1200.1, 1200.05 and 1058.01. For VA research, all regulations pertaining to the participation of veterans as participants including requirements for indemnification in case of research-related injury pertained to non-veteran participants enrolled in VA-approved research.

1.6 Federalwide Assurance (FWA)

The HRPP operates under the authority of its current Federalwide Assurance (FWA00005078) and has designated two IRBs (registered as 00000314 and 00002568) to review all human research protocols.

In its FWA, ORIC has opted to limit the application of the FWA to research funded by DHHS or federal agencies that have adopted the Common Rule.

1.7 Research Covered by the HRPP

The WVU HRPP covers all research involving human subjects that is under the auspices of WVU. The research may be externally funded, funded from WVU sources, or conducted without direct funding.

1.8 Written policies and procedures

The WVU Human Research Protections Policy and the HRPP Standard Operating Procedures detail the policies and regulations governing research with human subjects and the requirements for submitting research proposals for review by the WVU IRBs. This is not a static document. The policies and procedures are annually reviewed and revised by the Director of the Office of Research Integrity and Compliance (ORIC), the Institutional Review Board, and WVU Research Corporation (RC) General Counsel, or as need dictates. The Vice President for Research will approve all revisions of the policies and procedures.

The Director of the ORIC will keep the WVU research community apprised new information that may affect the Office of Research Integrity and Compliance, including laws, regulations, policies, procedures, and emerging ethical and scientific issues on its website and through campus electronic mailing lists. The policies and procedures will be available on the WVU IRB website and copies will be available upon request.

1.9 HRPP Organization

The HRPP is a comprehensive system to ensure the protection of human subjects participating in research. It consists of various individuals and committees such as: the Institutional Official, the Director of the ORIC, the IRB, other committees or subcommittees addressing human subjects protection (e.g., Biosafety, Protocol Review Monitoring Committee (PRMC), Conflict of Interest in Research), investigators, IRB staff, research staff, health and safety staff (e.g., Biosafety Officer, Radiation Safety Officer) and research pharmacy staff. The objective of this system is to assist the institution 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 implementing the HRPP:

1.9.1 Institutional Official

The ultimate responsibility for the WVU HRPP resides with the WVU Vice President for Research and Economic Development (VPR), who serves as the **Institutional Official (IO)** of the program. The IO is responsible for ensuring the WVU HRPP has the resources and support necessary to comply with all institutional policies and with federal regulations and guidelines that govern human subjects research. The IO is legally authorized to represent ORIC. He/she is the signatory of the FWA and assumes the obligations of the FWA.

The IO also holds ultimate responsibility for:

- oversight of the Institutional Review Boards (IRB);
- oversight over the conduct of research conducted by all WVU investigators;
- assuring the IRB members are appropriately knowledgeable to review research in accordance with ethical standards and applicable regulations;
- assuring that all investigators are appropriately knowledgeable to conduct research in accordance with ethical standards and applicable regulations;
- the development and implementation of an educational plan for IRB members, staff and investigators.

1.9.2 Director of the ORIC

The Director of the ORIC (Director) is selected by and reports to the Institutional Official (IO) and is responsible for:

1. Developing, managing and evaluating policies and procedures that ensure compliance with all state and federal regulations governing research. This includes monitoring changes in regulations and policies that relate to human research protection and overseeing all aspects of the HRPP program.
2. Advising the VPR (IO) on key matters regarding research at WVU.
3. Implementing the institution's HRPP policy.
4. Submitting, implementing and maintaining an approved FWA through the VPR and the Department of Health and Human Services Office of Human Research Protection (OHRP).
5. Managing the finances of the WVU HRPP.
6. Assisting investigators in their efforts to carry out WVU's research mission.
7. Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program.
8. Developing training requirements as required and as appropriate for investigators, subcommittee members and research staff, and ensuring that training is completed on a timely basis.

9. Serving as the primary contact at WVU Hospitals, Inc (WVUH) for the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services and other federal regulatory agencies.
10. Day-to-day responsibility for the operation of the ORIC, including supervision of HRPP staff.
11. Responding to faculty, student and staff questions.
12. Working closely with the Chairs of the IRBs and on the development of policy and procedures, as well as organizing and documenting the review process.

1.9.3 Institutional Review Board (IRB)

WVU IRB has two IRBs, appointed by the Institutional Official (IO). The IRBs prospectively review and make decisions concerning all human research conducted at WVU facilities, by its employees or agents, or under its auspices. The IRB is responsible for the protection of rights and welfare of human research subjects at WVU. It discharges this duty by complying with the requirements of the Common Rule; state regulations; the FWA; and institutional policies. (See Section 2 for a detailed discussion of the IRB)

1.9.4 Counsel's Office

The WVU HRPP relies on the WVU General Counsel and the WVU Research Corporation General Counsel for the interpretations and applications of West Virginia law and the laws of any other jurisdiction where research is conducted as they apply to human subject research.

The exception is research conducted by LAJVAMC which relies on the VA Regional Counsel for legal interpretation and application.

1.9.5 Department Chairs

Department Chairs in general are responsible for ensuring that the Principal Investigator (PI) is qualified by training and experience to conduct the proposed research. In addition, department chairs are responsible for ensuring that the PI has sufficient resources and facilities to conduct the proposed research. For each protocol submitted to the WVU IRB for approval, the department chair must certify that s/he accepts responsibility for assuring adherence to the federal and state regulations and institutional policies governing the protection of human subjects of research, including applicable institutional credentialing requirements.

Department chairs are required to review all proposals before they are submitted to the IRB for review. The signature of the Department Chair indicates that the study is found to be scientifically sound and can reasonably be expected to answer the proposed question.

Department chairs 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.

1.9.6 The Investigator

The investigator is the ultimate protector of the human subjects who participate in research. The investigator is expected to abide by the highest ethical standards and for developing a protocol that incorporates the principles of the Belmont Report. He/she is expected to conduct research in accordance with the approved research protocol and to oversee all aspects of the research by providing supervision of support staff, including oversight of the informed consent process. All subjects must give informed consent as required and the investigator must establish and maintain an open line of communication with all research subjects within his/her responsibility. In addition to complying with all the policies and standards of the governing regulatory bodies, the investigator must comply with institutional and administrative requirements for conducting research. The investigator is responsible for ensuring that all research staff completes appropriate training and must obtain all required approvals prior to initiating research. When investigational drugs or devices are used, the investigator is responsible for providing written procedures for their storage, security, dispensing and disposal.

1.9.7 Other Related Units

1.9.7.1 WVU Office of Sponsored Programs

Sponsored Programs staff reviews all research agreements with federal, foundation, or non-profit sponsors. This institutional review ensures that all terms of the award are in compliance with institutional 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 institution. As a further control, internal documents retained by Sponsored Programs as part of the application process for extramural funding include verification from the IRB whether a Data Safety Monitoring Plan (DSMP) is in place and the timelines associated with that DSMP will be given to the OSP.

When the grant or contract agreement includes human research activities that will be conducted by investigators who are not employees or agents of WVU, a subcontract is executed between WVU 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 by submission of an executed Form 310 (as applicable). The collaborating institution must also ensure that key personnel involved in human subjects 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 WVU.

1.9.7.2 WVU Pharmacy

A pharmacist from the WVU Department of Pharmaceuticals Services serves on each of WVU's IRBs, allowing the Pharmacy to have complete information about all IRB approved research that takes place at WVU WVUH and under its jurisdiction. The Pharmacist members assure that information about all studies involving drugs used in research is shared with both the Pharmacy Staff as appropriate and that the WVU Hospital Pharmacy and Therapeutics Committee is made aware of IRB approved research involving drugs.

The WVUH Pharmacy typically does not engage in the ordering/providing, dispensing, or compounding of drugs used in research, unless the drug is a controlled substance, in which case the item is ordered/received by the Pharmacy and re-issued in appropriate quantities to researchers for animal studies, or, for human studies, pursuant to a study-specific and patient-specific medication order developed by the Pharmacy in collaboration with the Researcher. The manufacture/compounding of drug products not commercially available is coordinated by the WVUH Pharmacy with outside Pharmacy vendors. However, insofar as inpatient drug studies and/or those outpatient drug studies that have subjects who become inpatients at WVUH, the Pharmacy coordinates the use of the study drug while the subject is an inpatient, and all such inpatient study drugs must be provided through the Pharmacy.

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

1.9.8 Relationship Between Components

The IRBs function independently of, but in coordination with, other institutional regulatory committees. The IRBs, however, make their independent determination whether to approve or disapprove a protocol based upon whether or not human subjects are adequately protected. The IRBs have review jurisdiction over all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency that has adopted the human subjects regulations.

The Compliance and Integrity Committee will meet to ensure a dialogue is maintained between the various compliance entities at the Organization. Membership is comprised of the Office of Sponsored Programs (OSP) Director, ORIC Director, the Vice President for Research (WVU IO) and two or more additional members who may be employees of West Virginia University or members of the public who are not employees of WVU. The committee will act in an advisory capacity to the Vice President for Research, monitoring the effectiveness of existing compliance programs, developing new or revised policies as changes in requirements occur, and disseminating updated compliance information to the research community.

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

1.9.8.1 Protocol-specific coordination

The **Initial Application** form, which must be submitted with every protocol, requires PIs to indicate institutional support required for the research, including:

- Laboratory
- Medicine
- Pharmacy
- Radiology
- Nuclear Medicine
- Nursing
- Psychiatry
- Outpatient
- Surgery
- Other

For any that are indicated, a letter of support or collaboration must be included and the designated signatory for the required service must sign the form. The protocol will be reviewed in the ORIC to ensure that all necessary letters are included.

1.10 HRPP Operations

In addition to the leadership structure described above, other support staff members for the HRPP include four staff members and one part-time student worker. The HRPP Staff for HRP Associates must comply with all ethical standards and practices.

1.10.1 Office of Research Integrity and Compliance (ORIC)

The WVU HRPP reports to the Director of the Office of Research Integrity and Compliance (ORIC), who has day-to-day responsibilities for its operations.

Additionally, the office is staffed by a Senior Program Coordinator, Senior Administrative Assistant, and two Administrative Associates. The duties and responsibilities for all staff are found in their respective job descriptions, and their performance is evaluated on an annual basis.

1.10.2 Senior Program Coordinator (SPC) and Senior Administrative Assistant (SAA)

The SPC and SAA are responsible for all aspects of the IRB throughout the review process of a research proposal involving human subjects. This responsibility includes the initial review of documents and screening of research proposals prior to its review by the IRB, as well as serving as the liaison between the investigators and the IRB. The SPC and SAA review the IRB minutes for accuracy and ensures proper documentation of discussions, including controverted issues and actions taken by the IRB during its convened meetings.

1.10.3 Administrative Associates (AA)

The AAs are responsible for providing administrative and clerical support to the IRB Chair and SPC and SAA as well as scheduling and coordinating all IRB functions. The IRB AAs are also responsible for IRB record retention. The AAs are responsible for maintaining complete IRB files, records of all research protocols, IRB correspondence (including e-mails), as well as Research Credentialing records of investigators and research staff.

1.10.4 Selection, Supervision and Evaluation of HRPP Supporting Staff

Selection Process

All HRPP staff who support the IRB and ORIC are selected by the Director under WVU Human Resources policies and procedures.

Depending on the position to be filled, qualification to be considered in the selection of HRPP staff include prior experience in IRB administration or another position within an HRPP (e.g., study coordinator), or, at the assistant or clerical levels, a desire to learn and be an active participant in the regulatory, ethical, and procedural aspects that support an HRPP.

Supervision

HRPP staff is supervised by the ORIC Director.

Evaluation

HRPP staff is evaluated on an annual basis consistent according to WVU Human Resources policies and procedures.

1.11 HRPP Resources

The ORIC is located in offices at 886 Chestnut Ridge Road and is equipped with all the necessary office, meeting, storage space and equipment to perform the functions required by the HRPP. The adequacy of personnel and non-personnel resources of the HRPP program is assessed on an annual basis by the Director with the HRPP staff and are reviewed and approved by the IO.

The WVU Institutional Official provides resources to the IRB and ORIC, including adequate meeting and office space, and staff for conducting IRB business. Office equipment and supplies, including technical support, file cabinets, computers, internet access, and copy machines, will be made available to the IRB and staff. The resources provided for the IRB and ORIC will be reviewed during the annual budget review process.

1.12 Conduct of Quality Assurance/Quality Improvement Activities

The objective of the Organization's HRPP Quality Assurance / Quality Improvement Plan is to measure and improve human research protection effectiveness, quality, and

compliance with organizational policies and procedures and applicable federal, state, and local laws. The Quality Assurance / Quality Improvement Plan will be managed and implemented by an individual in a compliance role.

1.12.1 Investigator Audits and Compliance Reviews

Directed (“for cause”) audits and periodic (not “for cause”) compliance reviews will be conducted to assess investigator compliance with federal, state, and local law, and Organization policies, and to identify areas for improvement, and suggest recommendations based on existing policies and procedures. Directed audits of IRB-approved research studies are in response to identified concerns. Periodic compliance reviews are conducted using a systematic method to review IRB-approved research on a regular basis. The results will be reported to the Director and the IRB Chair.

Activities of auditors during directed audits and periodic compliance reviews may include:

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

Annually, the Director defines at least one targeted measure of compliance within the HRPP. **Goal Tracking Form 1: Annual Goals for Achieving Targeted Levels of Quality, Efficiency, and Effectiveness** is the document which is used to define and measure compliance with these annual goals. In order to evaluate whether the defined goals are being achieved, the compliance officer collects and records compliance data stemming from the activities listed in items a-i above each quarter. The data is then logged into the Goal Tracking Form for tracking purposes. At the end of each fiscal year, the Director evaluates whether the respective goals were achieved and adjusts the affected processes to correct any deficiencies.

1.12.2 External Site Audits and Compliance Reviews

External directed audits and periodic compliance reviews will be conducted at non-Organization sites, where the Organization’s IRBs serve as the “IRB of Record,” to

assess compliance with federal, state, and local law, research subject safety, and IRB policies and procedures. These reviews may include items listed in section 1.12.1 above.

1.12.3 Reporting and Disposition

The results of all quality assurance activities are reported to the Director and the IRB Chairs. Any noncompliance will be handled according to the procedures in Section 10 of the WVU Human Research Protections Program Policies and Procedures.

If an audit or review finds that subjects in a research project have been exposed to unexpected serious harm, the reviewer will promptly report such findings to the Director and the IRB Chairs for immediate action.

1.12.4 HRPP Internal Compliance Reviews

Internal directed audits and random internal compliance reviews will be conducted. The results may impact current practices and may require additional educational activities, and will be reported to the Director. The IRB Auditor will:

- a) Review 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 other risk/benefit ratio and consent issues that are included in the criteria for approval;
- b. Assess the IRB minutes to assure that quorum was met and maintained;
- c) Assess the current adverse event reporting process;
- d) Assess privacy provisions, according to HIPAA, have been adequately reviewed, discussed and documented in the IRB minutes;
- e) Evaluate the continuing review discussions to assure they are substantive and meaningful and that no lapse has occurred since the previous IRB review;
- f) Observe IRB meetings or other related activities;
- g) Review IRB files to assure retention of appropriate documentation and consistent organization of the IRB file according to current policies and procedures;
- h) Review the IRB database to assure all fields are completed accurately;
- i) Review of evaluations by the IRB members;
- j) Verification of IRB approvals for collaborating institutions or external performance sites;
- k) Review the appropriate metrics (for example, time from submission to first review) to evaluate the quality, efficiency, and effectiveness of the IRB review process;
- l) Review the workload of IRB staff to evaluate appropriate staffing level;
- m) Other monitoring or auditing activities deemed appropriate by the IRB

The Director will review the results of internal compliance reviews with the IRB Chair and the Institutional Official. If any deficiencies are noted in the review, a corrective action plan will be developed by the Director 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.

Annually, the Director defines at least one targeted measure of operational efficiency and effectiveness within the HRPP. **Goal Tracking Form 2: Annual Goals for Achieving Targeted Levels of Compliance within the HRPP** is the document which is used to define and measure compliance with these annual goals. In order to evaluate whether the defined goals are being achieved, the compliance officer collects and records compliance data stemming from the activities listed in items a-m above each quarter. The data is then logged into the Goal Tracking Form for tracking purposes. At the end of each fiscal year, the Director evaluates whether the respective goals were achieved and adjusts the affected processes to correct any deficiencies.

1.12.5 Quality Improvement

All quality assurance reports, both research-related and HRPP -related, will be reviewed by the Director and the Institutional Official in order to determine if systemic changes are required in the HRPP to prevent re-occurrence. If so, a corrective action plan will be developed, implemented and evaluated by the Director and Institutional Official (IO).

1.13 Collaborative Research Projects

In the conduct of cooperative research projects, WVU acknowledges that each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations. When a cooperative agreement exists, WVU may enter into a joint review arrangement, rely on the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort. A formal relationship must be established between WVU and the other institution through either a Cooperative Agreement or a Memorandum of Understanding. This relationship must be formalized before WVU will accept any human research proposals from the other institution or rely on the review of the other institution.

It is the policy of WVU to assure that all facilities participating in a human subjects study 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 IRBs of record for each participating facility and, where appropriate, the IRB of record for the coordinating facility.

For collaborative research, the PI must identify all institutions participating in the research, the responsible IRB(s), and the procedures for dissemination of protocol information (IRB initial and continuing approvals, relevant reports of unanticipated problems, protocol modifications, and interim reports) between all participating institutions.

When WVU relies on another IRB, the Director of ORIC will review the policies and procedures of the IRB to ensure that they meet WVU standards. If the other IRB is part of an accredited organization, then it will be assumed that the WVU standards are being met.

When WVU reviews research conducted at another institution, the particular characteristics of each institution's local research context must be considered, either (i) through knowledge of its local research context by a WVU IRB or (ii) through subsequent review by appropriate designated institutional officials, such as a Chairperson and/or other IRB members.

If WVU is the coordinating facility the Principal Investigator must document how the important human subject protection information will be communicated to the other participating facilities engaged in the research study. The investigator is responsible for serving as the single liaison with outside regulatory agencies, with other participating facilities, and for all aspects of internal review and oversight procedures. The investigator is responsible for ensuring that all participating facilities obtain review and approval from their IRB of record and adopt all protocol modifications in a timely fashion. The investigator is responsible for ensuring that the research study is reviewed and approved by any other appropriate committees at the coordinating facility and at the participating facilities (e.g. VA Research and Development Committee approval) prior to enrollment of participants.

The PI must follow these procedures when WVU is the coordinating facility:

- 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 WVU is the coordinating facility of a multi-site study.
- The investigator submits the following information in their IRB application materials:
 - Whether research activities at participating institutions are defined as engagement
 - Name of each participating facility
 - Confirmation that each participating facility has an FWA (including FWA number)
 - Contact name and information for investigator at each participating facility
 - Contact name and information for IRB of record at each participating facility
 - Method for assuring all participating facilities have the most current version of the protocol
 - Method for confirming that all amendments and modifications in the protocol have been 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
- The investigator submits approval letters from all the IRB of record for all participating sites.

- The investigator maintains documentation of all correspondence between participating sites and their IRBs of record.

 <p>West Virginia University Human Research Protections Program (HRPP) Office of Research Integrity & Compliance STANDARD OPERATING PROCEDURES</p>	<p>Section #: 2 Title: <i>Institutional Review Board</i> Date: December 10, 2010 Page: Page 29 of 194</p>
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2 Institutional Review Board

WVU has established two on-site Institutional Review Boards (IRB) to ensure the protection of human subjects in human subjects research conducted under the auspices of WVU. All non-exempt human subjects research conducted under the auspices of WVU must be reviewed and approved by a WVU IRB prior to the initiation of the research.

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

WVU Associates also utilizes the services National Cancer Institute's Central Institutional Review Board (NCI CIRB) for applicable cooperative oncology group

The NCI CIRB serves as an IRB-of-record for WVA and has the same authority as the on-site IRBs and all determinations and findings of the NCI CIRB are equally binding on all research under the auspices of the institution. Procedures for the NCI CIRB are found in Section 3.15.

The following describes the authority, role and procedures of the on-site IRB.

2.1 IRB Authority

The IRB derives its authority from the WVU policy. Under the Federal Regulations, the IRBs authority includes:

1. To approve, require modifications to secure approval, or disapprove all research activities overseen and conducted under the auspices of WVU;
2. 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;
3. To observe, or have a third party observe, the consent process; and
4. To observe, or have a third party observe, the conduct of the research.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the institution. However, those officials may NOT approve

research if it has not been approved by the IRB. WVU officials may strengthen requirements and/or conditions, or add other modifications to secure WVU approval or approval by another WVU committee. Previously approved research proposals and/or consent forms must be re-approved by the IRB before initiating the changes or modifications.

2.2 Number of IRBs

There are currently two on-site IRBs. The IO, the Director, and the Chairs of the IRBs will review the activity of the two IRBs on at least an annual basis and make a determination as to the appropriate number of IRBs that are needed for the institution. This determination will be based on the evaluation of the performance of IRB as described in Section 1.14.4.

2.3 Roles and Responsibilities

2.3.1 Chair of the IRB

The WVU Institutional Official (IO), in consultation and approval with the IRB members, and the Director of ORIC, appoints a Chair and Vice Chair of each IRB to serve for renewable three-year terms. Any change in appointment, including reappointment or removal, requires written notification.

The IRB Chairs should be highly respected individuals, from WVU or the community, 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 institutional community will fall primarily on the shoulders of the Chairs. The IRBs must be perceived to be fair, impartial and immune to pressure by the institution's administration, the investigators whose protocols are brought before it, and other professional and nonprofessional sources.

The IRB Chair is responsible for conducting the meetings and is a signatory for correspondence generated by the HRPP.

The IRB Chair may designate other IRB members to perform duties, as appropriate, for review, signature authority, and other IRB functions, e.g., the Vice Chair and Director of the ORIC.

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

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

2.3.2 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 Chair.

2.3.3 Subcommittees of the IRB

The IRB Chair, in consultation with the Director may designate one or more other IRB subcommittees of the IRB to perform duties, as appropriate, to review and undertake other IRB functions, and to make recommendations to the IRB for Research that is not Expedited. The IRB Chair, in consultation as needed with the 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 authority delegated by the IRB Chair to such IRB Subcommittee (e.g., merely making recommendations versus decision-making authority). Members of the IRB Subcommittee must be experienced in terms of seniority on the IRB, and must be matched as closely as possible with their field of expertise to the study assigned to the IRB Subcommittee.

If the IRB Chair creates one or more IRB Subcommittees, he/she shall also indicate whether it is a standing or *ad hoc* IRB Subcommittee.

2.4 IRB Membership

IRB members are selected based on appropriate diversity, including consideration of race, gender, cultural backgrounds, specific community concerns in addition to representation by multiple, diverse professions, knowledge and experience with vulnerable subjects, and inclusion of both scientific and non-scientific members. The structure and composition of the IRB must be 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 WVU. WVU has procedures (See Section 4) that specifically outline the requirements of protocol review by individuals with appropriate scientific or scholarly expertise.

In addition, the IRB will include members who are knowledgeable about and experienced working with vulnerable populations that typically participate in WVU research.

No one from the WVU Office of Sponsored Programs or Office of Technology Transfer shall 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 guests.

VA Research and Development administration officials including, but not limited to the Associated Chief of Staff for Research and Development and the Administrative Officer for Research and Development, are prohibited from serving as voting members of these panels.

The IRB must promote respect for its advice; counsel in safeguarding the rights and welfare of human subjects; and possess the professional competence necessary to review specific research activities. A member of the IRB may fill multiple membership position requirements for the IRB.

2.5 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 WVU.
2. The IRB will be sufficiently qualified through the experience, expertise, and 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 institutional policies 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. When protocols involve vulnerable populations, the review process will include one or more individuals who are knowledgeable about or experienced in working with these participants, either as members of the IRB or as consultants (see Section 2.9).
5. Every nondiscriminatory effort will be made to ensure that the IRB does not consist entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. The IRB shall not consist entirely of members of one profession.
6. The IRB must include 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 must include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.
8. The IRB includes at least one member who represents the general perspective of participants.
9. The IRB must include two or more LAJVAMC employees as voting members of the IRB. At least one of these members must have scientific expertise. The

members must serve as full members of the IRB; this includes reviewing non-VA research matters coming before the IRB. At least one of the VA members of the IRB must be present during the review of VA research

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

11. The Director and administrators of the ORIC may be voting members of the IRB.

On an annual basis, the IRB Chairs and the Director shall review the membership and composition of the IRB to determine if they continue to meet regulatory and Institutional requirements. Required changes in IRB membership will be reported to the OHRP.

2.6 Appointment of Members to the IRB

The IRB Chair, Vice Chair and/or the Director of the ORIC, identifies a need for a new, replacement, or alternate member. The IRB may nominate candidates and send the names of the nominees to the ORIC. Department Chairs and others may forward nominations to the Institutional Official, or to the ORIC, or to an IRB Chair.

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

Appointments are made for a renewable three-year period of service. Any change in appointment, including reappointment or removal, requires written notification. Members may resign by written notification to the Chair.

The Director of the LAJVAMC will officially appoint LAJVAMC representatives to the IRBs of record in writing. The LAJVAMC representatives will be appointed for a period of 3 years and may be re-appointed indefinitely.

On an annual basis, the IRB Chair and the Director of the ORIC review the membership and composition of the IRB to determine if they continue to meet regulatory and institutional requirements.

2.7 Alternate members

In general, the members of each IRB act as alternates for the other IRB. However, whenever there is a need because of unique expertise, the appointment and function of alternate members is the same as that for primary IRB members, and the alternate's expertise and perspective are 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) for whom each alternate member may substitute. The alternate member will not be counted as a voting member unless the primary member is absent. The IRB minutes will document when an alternate member replaces a primary member.

2.8 IRB Member Conflict of Interest

No regular, alternate, or ex officio member may participate in the review (initial, continuing, or modification) 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 voting and non-voting member to disclose any COI in a study submitted for review and recuse him/herself from the deliberations and vote by leaving the room.

All voting, alternate, and ex officio members of the IRB complete a “WVU Conflict of Interest Research Disclosure Form” when first appointed and annually thereafter. If a member responds affirmatively to the existence of a potential conflict, the COIR Officer is notified. [See Section 104 “Conflicts of Interest in Research” for a detailed description of managing conflicts of interest.]

Committee members may find themselves in any of the following conflicts of interest when reviewing research:

1. Where the member or consultant is involved in the design, conduct, and reporting of the research.
2. Where an immediate family member of the member or consultant is involved in the design, conduct, and reporting of the research.
3. Where the member holds significant financial interests (See 14.1 for a definition of significant financial interests) related to the research being reviewed
4. Any other situation where an IRB member believes that another interest conflicts with his or her ability to deliberate objectively on a protocol.

The IRB Chair will poll IRB members at each convened meeting to determine if a COI exists regarding any protocols to be considered during the meeting and reminds them that they should recuse themselves by leaving the room during the discussion and vote on the specific protocol. IRB members with a conflicting interest are excluded from being counted towards quorum. All recusals by members with COI are recorded in the minutes.

If the Conflict of Interest status of an IRB member changes during the course of a study, the IRB member is required to declare this to the IRB Chair and/or Director of the ORIC

2.9 Use of Consultants

When necessary, the IRB Chair or the Director of the ORIC may solicit individuals from the Organization or the community with competence in special areas to assist in the review of issues or protocols, which require appropriate scientific or scholarly expertise beyond or in addition to that available on the IRB. The need for an outside reviewer is determined in advance of the meeting by the Director or the Chair by reviewing the protocols scheduled to be reviewed at the convened meeting. The ORIC will ensure that all relevant materials are provided to the outside reviewer prior to the convened meeting.

Written statements of consultants will be kept in 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 protocol.

The Director of the ORIC reviews the conflicting interest policy for IRB members (2.8) with consultants and consultants must verbally confirm to the Director of the ORIC that they do not have a conflict of interest prior to review. Individuals who have a conflicting interest or whose spouse or 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 full board for consideration either in person or in writing. If in attendance, these individuals will provide consultation but may not participate in or observe the vote.

Ad hoc or informal consultations requested by individual members (rather than the full board) will be requested in a manner that protects the researcher's confidentiality and is in compliance with the IRB conflict of interest policy (unless the question raised is generic enough to protect the identity of the particular PI and research protocol).

2.10 Duties of IRB Members

The agenda, submission materials, protocols, proposed informed consent forms and other appropriate documents are distributed electronically to members prior to the convened meetings at which the research is scheduled to be discussed. Members review the materials at least one week before each meeting, in order to participate fully in the review of each proposed project. IRB members will treat the research proposals, protocols, and supporting data confidentially. All copies of the protocols and supporting data are returned to the IRB staff at the conclusion of the review for professional document destruction.

2.11 Attendance Requirements

Members should attend all meetings for which they are scheduled. If a member is unable to attend a scheduled meeting, they should inform the IRB Chair, Vice Chair, or an ORIC staff member. If the inability to attend will be prolonged, a request for an alternate to be assigned may be submitted to the Chair or the Director.

If an IRB member is to be absent for an extended period of time, such as for a sabbatical, he or she must notify the IRB at least 30 days in advance so that an appropriate replacement can be obtained. The replacement can be temporary, for the period of absence, or permanent if the member is not returning to the IRB. If the member has a designated alternate (See Section 5.3), the alternate can serve during the primary member's absence, provided the IRB has been notified in advance.

2.12 Training / Ongoing Education of Chair and IRB Members in Regulations, Procedures

A vital component of a comprehensive Office of Research Integrity and Compliance is an education program for IRB Chair and the IRB members. WVU is committed to providing training and an on-going educational process for IRB members and the staff

of the ORIC related to ethical concerns and regulatory and institutional requirements for the protection of human subjects.

Orientation

New IRB members, including alternate members will meet with the Director for an informal orientation session. At the session, the new member will be given an IRB Research Sheet (binder) that indicates where the following can be found:

- Belmont Report;
- WVU Policies and Procedures for the Protection of Human Subjects;
- Federal regulations relevant to the IRB

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

Initial Education

IRB members will complete the required modules in the CITI Course in the Protection of Human Research Subjects, including the IRB Member Module - "What Every New IRB Member Needs to Know".

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 staff must also satisfy continuing education requirements on an annual basis. ORIC uses the following activities as a means for offering continuing education to IRB members and staff:

- In-service training at IRB meetings;
- Training workshops;
- Copies of appropriate publications; via hard copy electronically;
- Identification and dissemination by the Director of new information that might have affected the Office of Research Integrity and Compliance , including laws, regulations, policies, procedures, and emerging ethical and scientific issues to IRB members via email, mail, or during IRB meetings;
- Unlimited access to the ORIC resource library.

IRB members and staff are also required to complete CITI training every 3 years as part of WVU's continuing education requirements.

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 activities for continuing education vary on a yearly basis depending on operating budget and areas of need, as determined by the Director. The Director determines which continuing education activities are mandatory for IRB members and staff in a given year and tracks whether each individual has satisfied the requirements. IRB members who have not fulfilled their continuing education requirements will not be allowed to attend IRB meetings until they are fulfilled. Continuing noncompliance will result in the individual not being renewed as an IRB member.

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

The HRPP Professional Staff is required to complete the entire CITI Course in the Protection of Human Research Subjects. Staff will be expected to attend OHRP training or some other resource at least annually. For members of the IRB staff who do not satisfy continuing education requirements, this will be evaluated as part of the individual's annual performance review.

2.13 Liability Coverage for IRB Members

The Organization's insurance coverage applies to employees and any other person authorized to act on behalf of the Organization or acts or omissions within the scope of their employment or authorized activity.

2.14 Review of IRB Member Performance

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

2.15 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 Institutional Official (IO), depending on the circumstances. The official receiving the report will conduct a thorough investigation and corrective action will be taken to prevent additional occurrences.

 <p>West Virginia University Human Research Protections Program (HRPP)</p> <p>Office of Research Integrity & Compliance</p> <p>STANDARD OPERATING PROCEDURES</p>	<p>Section #: 3</p> <p>Title: <i>IRB Review Process</i></p> <p>Date: December 10, 2010</p> <p>Page: Page 39 of 194</p>
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3 IRB Review Process

All human subjects research conducted under the auspices of WVU must meet the criteria for one of the following methods for review:

- Exempt
- Expedited Review
- Full Committee Review

The IRB will ensure that the research meets all required ethical and regulatory criteria for initial and continuing review and any modifications of approved research.

The following describe the procedures required for the review of research by the on-site IRB.

3.1 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 level of risks to subjects
2. the research design or methodology (adding procedures that are not eligible for expedited review [See Section 3.4] would not be considered a minor change)
3. the number of subjects enrolled in the research (no greater than 10% of the total requested)
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 simple majority of the voting membership, including at least one member whose primary concern is in a non-scientific area. If research involving an FDA-regulated article is involved, a licensed physician must be included in the quorum.

Suspension of IRB approval. A suspension is a directive of the convened IRB or other authorized individual (See Section 10) to temporarily stop some or all previously approved research activities. Suspended protocols remain open and require continuing review.

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

3.2 Human Subjects Research Determination

The responsibility for initial determination as to whether an activity constitutes human subjects research rests with the investigator. The investigator should make this determination based on the definitions of “human subject” and “research” in Section 1.4. Since the Organization will hold them responsible if the determination is not correct, investigators are urged to request a confirmation that an activity does not constitute human subjects research from the ORIC. The request may be made verbally, by phone contact, by email or through a formal written communication. All requests must include sufficient documentation of the activity to support the determination.

Determinations as to whether an activity constitutes human subjects research will be made according to the definitions in Section 1.3 using the **Human Subjects Research Determination Checklists**. Determinations regarding activities that are either clearly or clearly not human subjects research, based on the checklists, may be made by the IRB Manager. Determinations regarding less clear-cut activities will be referred to the IRB Chair, who may make the determination or refer the matter to the full IRB.

Documentation of all determinations made through the ORIC will be recorded and maintained in the ORIC. Formal submissions will be responded to in writing and a copy of the submitted materials and determination letter/email will be kept on file.

3.3 Exempt Studies

All research using human subjects must be approved by the Institution. Certain categories of research (i.e., “exempt research”) do not require convened IRB review and approval. Exempt research is subject to institutional review and must be determined and approved by the IRB Chair or his/her designee.

3.3.1 Limitations on Exemptions

Children: Exemption for research involving survey or interview procedures or observations of public behavior 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.

3.3.2 Categories of Exempt Research

With the above exceptions, research activities not regulated by the FDA (see Section 3.3.3 for FDA Exemptions) in which the only involvement of human subjects will be in one or more of the following categories are exempt from IRB review, but require institutional review:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as
 - a) research on regular and special education instructional strategies, or
 - b) 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:
 - a) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
 - b) 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:
 - a) the human subjects are elected or appointed public officials or candidates for public office; or
 - b) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information 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.

Please see section 3.3.6 for additional clarification of studies involving the collection of medical records that may also fall under this category (exemption category 4).

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:
 - a) Public benefit or service programs;
 - b) Procedures for obtaining benefits or services under those programs;
 - c) Possible changes in or alternatives to those programs or procedures; or
 - d) Possible changes in methods or levels of payment for benefits or services under those programs.
 - e) 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 American Act).
 - f) 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 funding agency.
6. Taste and food quality evaluation and consumer acceptance studies,
 - a) If wholesome foods without additives are consumed; or
 - b) 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 Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

3.3.3 FDA Exemptions

The following categories of clinical investigations are exempt from the requirements of 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)]

Note: See Section 7.4.3 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 Food and Drug Administration 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)]

3.3.4 Procedures for Exemption Determination

In order to obtain an exemption determination investigators must submit:

1. a completed **Request for Exemption** form;
2. all recruitment materials (e.g., letter of invitation, recruitment script, flyer),
3. consent form (when appropriate),
4. all surveys, questionnaires, instruments, etc.,
5. letter(s) of permission from each non-Organization site of performance
6. if sponsored, one copy of the grant application(s) and/or contract
7. verification of current human research protection training for all members of the research team, including the faculty advisor

The IRB Chair (or designee) reviews all requests for exemptions and determines whether the request meets the criteria for exempt research. The IRB Chair may designate an IRB member to review requests for exemptions submitted to the IRB. The Chair selects designees who are qualified to review this category of submission based on their expertise of the protocol content and knowledge of regulations pertaining to research. If there is not a designated reviewer to consider requests for exemptions, the IRB Chair reviews the requests. Individuals involved in making the determination of an IRB exempt status of a proposed research project cannot be involved in the proposed research. Reviewers do not have any apparent conflict of interest.

To document the IRB reviewer's determination of the request for exempt research, he/she completes the Exemption Determination Form. The IRB reviewer verifies on the form whether the submission meets the definition for "research" or "clinical investigation". If the request meets the definitions of both human subject and research, the reviewer indicates whether the request for exemption was approved or denied, and if approved, the rationale for the determination and category under which it was permitted.

Investigators will be given feedback either by phone or email as to the qualification of the application for exempt status. Once institutional review is completed, IRB staff will send an email and electronic acknowledgement to the PI of the results of the review.

Exempt studies are communicated to the IRB at the next convened meeting after the approval of exemption.

All requests for an exemption must include a termination date. The exemption is only good until that date or three years, whichever comes first. If the research extends beyond that date then the researcher has to request another exemption or a renewal. The decision must be communicated in writing to the investigator and the IRB. Documentation must include the specific categories justifying the exemption.

VA research projects that are determined exempt must be reviewed by the LAJVAMC R&D Committee prior to initiation and then they must be included in its annual review of research projects. For questions contact the VA Research Office.

3.3.5 Additional Protections

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.

3.3.6 Clarification of Exemption Category Four Review for Studies Involving the Collection of Data from Medical Records

Research studies involving the collection of data from medical records may qualify as exempt from review under category four provided that the following criteria are met:

1. The data must exist at the time of the exemption application. Studies wishing to collect data from the medical records of patients who have ***not yet been seen*** clinically would not qualify for exemption.
2. The data must be recorded without codes or links to patient identifiers (i.e., the medical record number (MRN)). For example, researchers often obtain a list of MRNs from patients with a specific condition being studied that they then use to locate medical records for the purposes of data collection. As long as no code or link is assigned to each patient that would allow linkage of the collected data and the specific medical record, this type of research may qualify for exemption. However, researchers wishing to assign such a link to enable revisiting of the medical record would need to apply for expedited approval. A HIPAA application should be submitted for both review types (exempt and expedited), and a consent form waiver will need to be submitted for medical records research not qualifying as exempt category four.

3.4 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

3.4.1 Categories of Research Eligible for Expedited Review

[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.

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 governmental classified research involving human subjects.

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

Research Categories one (1) through seven (7) pertain to 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: However, the WVU IRB has determined that all drug studies must receive full board 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 children¹, 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. [1Children are defined in the DHHS regulations 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."][45
CFR 46.402(a)]

(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.

(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. (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)(4). 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.]

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

(a) where (i) the research 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; or (b) where no subjects have been enrolled and no additional risks have been

identified; or (c) where the remaining research activities are limited to data analysis.

[Of note, category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed by a convened IRB may undergo subsequent continuing review by the expedited review procedure.

For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8)(a), (b), or (c) are satisfied for that site. However, with respect to category 8(b), while the criterion that "no subjects have been enrolled" is interpreted to mean that no subjects have ever been enrolled at a particular site, the criterion that "no additional risks have been identified" is interpreted to mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.]

(9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

[Under Category (9), an expedited review procedure may be used for continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories (2) through (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified. The determination that "no additional risks have been identified" does not need to be made by the convened IRB.]

3.4.2 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.

On an annual basis, 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 of the IRB. The IRB Staff will select expedited reviewers from that list. Selected reviewers will have the qualifications, experience and knowledge in the content of the protocol 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 2.8) will not be selected.

When reviewing research under an expedited review procedure, the IRB Chair, or designated IRB member(s), should receive and review all documentation that would normally be submitted for a full-board review including the complete protocol, a Continuation review form summarizing the research since the previous review (including modifications and unanticipated problems), notes from the pre-screening conducted by

the ORIC staff, the current consent documentation and determine the regulatory criteria for use of such a review procedure by using the **Expedited Review Checklists**.

The reviewer(s) conducting initial or continuing review complete the appropriate **“Institutional Review Board - Protocol Review”** checklists to determine whether the research meets the criteria allowing review using the expedited procedure and if so, whether the research meets the regulatory criteria for approval. 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 protocol will be placed on the next agenda for an IRB meeting.

In reviewing the research, the reviewers will follow the Review Procedures described in Sections 3.4 & 3.6 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 set forth below.

Reviewers will indicate approval, required modifications or requirement for convened board review on the Protocol Review/Initial Review and return to the ORIC. If modifications are required the ORIC staff will inform the investigator by e-mail.

In the event that expedited review is carried out by more than one IRB member and the expedited reviewers disagree, the IRB Director and/or IRB Chair may make a final determination. Upon the discretion of the IRB Director or IRB Chair the protocol will be submitted to the IRB for review.

3.4.3 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 the full protocol by contacting the ORIC.

3.5 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.

3.5.1 IRB Meeting Schedule

The IRB meets on a regular basis throughout the year (usually once per month.) The schedule for the IRB may vary due to holidays or lack of quorum. The schedule for IRB meetings may be found on the ORIC website. Additionally, this information is available in the ORIC and is posted for the benefit of all investigators, research coordinators and other research staff when submitting protocol materials. Special meeting may be called at anytime by the Chairs or the Director.

3.5.2 Preliminary Review

The Senior Program Coordinator or Senior Administrative Assistant (IRB Managers) will perform a preliminary review of all protocol materials submitted to the ORIC for

determination of completeness and accuracy, including informed consent checklists. Only complete submissions will be placed on the IRB agenda for review. The investigator will be informed either by the electronic system of missing materials and the necessary date of receipt for inclusion on that month's agenda. In the case of a PI who is submitting a protocol for the first time or an investigator who may not be well-versed in the protocol submission procedures, individualized IRB consultations can be arranged. Specific questions about the IRB policies and procedures, determination of whether a particular protocol is human research or not and what particular forms are required for a particular study can be submitted in writing to the IRB manager for information and/or clarification. Individual appointments with the IRB Manager can also be arranged and are strongly recommended for first-time submissions.

3.5.3 Primary and Secondary Reviewers

After it has been determined that the protocol submission is complete, the IRB Managers will assign protocols for review paying close attention to the scientific content of the protocol, the potential reviewer's area of expertise and representation for vulnerable populations involved in the research. One reviewer will be assigned to each protocol and a reviewer may be assigned several protocols or other research items for review. Reviewers are assigned to all protocols requiring initial review, continuing review, and modifications. When the IRB is presented with a protocol which may be outside of the knowledge base or representative capacity of all of the IRB members, an outside consultant will be sought. (See item 2.9 above). Protocols for which appropriate expertise cannot be obtained for a given meeting will be deferred to another meeting when appropriate expertise can be achieved.

The 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. Leading the discussion of the proposed research at the convened meeting, presenting both positive and negative aspects of the research, and leading the IRB through the regulatory criteria for approval (See Section 3.6).
4. Making suggestions for changes to the proposed research, where applicable.
5. Completing all applicable IRB reviewer forms.

If both the primary and secondary reviewer are absent from the meeting, a new reviewer may be assigned, providing the new reviewer has reviewed the materials prior to the meeting. Additionally, an absent reviewer can submit their written comments for presentation at the convened meeting, as long as there is another reviewer present at the convened meeting, who can serve as the primary reviewer. It should be noted that all of the IRB members receive and is expected to review all studies, not just the ones they are responsible for reviewing.

3.5.4 Pre-Meeting Distribution of Documents

All required materials need to be submitted (in full) 5 business days prior to the convened meeting for inclusion on the following IRB agenda. The meeting agenda will be prepared by the IRB managers and distributed to the IRB members prior to the meeting. All IRB members receive their review materials which include the IRB agenda, prior month's meeting minutes, applicable business items and audits, appropriate continuing education materials and protocol review materials electronically no later than 5 business days before the scheduled meeting to allow sufficient time for the review process.

3.5.5 Materials received by the IRB

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

- Complete Protocol Application form
- Proposed Consent / Parental Permission / Assent Form(s)
- Recruitment materials / subject information
- Data collection instruments (including all surveys and questionnaires)

At least one primary reviewer must receive and review: Any relevant grant applications; the sponsor's protocol (when one exists); the investigator's brochure (when one exists); the DHHS-approved sample informed consent document (when one exists); the complete DHHS-approved protocol (when one exists).

Any IRB member may request any of the material provided to the primary and secondary reviewers by contacting the ORIC.

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

Protocol reviewers will use the WVU Protocol Review Checklists as a guide to completing their review.

3.5.6 Quorum

A quorum consists of a simple majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area. If research involving an FDA-regulated article is involved, a licensed physician must be included in the quorum. At least one of the LAJVAMC VA members of the Board must be present during the review of VA research.

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 an appropriate 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, the pending action item must be deferred or the meeting terminated. The IRB Staff will document the time of arrival and departure for all IRB members and notify the IRB Chair if a quorum is not present. A quorum worksheet is electronically completed by the IRB Staff and/or IRB Chair to determine and document attendance and whether the IRB meeting is appropriately convened and maintained. The IRB Coordinator for each meeting will electronically track each IRB member during the meeting.

It is generally expected that at least one unaffiliated member and at least one member who represents the general perspective of participants (the same individual can serve in both capacities) will be present at all IRB meetings. Although the IRB may, on occasion, meet without this representation, individuals serving in this capacity must be present for at least 80% of the IRB meetings.

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. When 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, voicemail, text messaging, 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.

3.5.7 Meeting Procedures

The IRB Chair, or Vice-Chair in the event that the IRB Chair is absent, will call the meeting to order, once it has been determined that a quorum is in place. The Chair or Vice-Chair will remind IRB members to recuse themselves from the discussion and vote by leaving the room when there is a conflict. The IRB will review and discuss the IRB Minutes from the prior meeting and determine if there are any revisions/corrections to be made. If there are no changes to be made, the Minutes will be accepted as presented and considered final. If it is determined that revisions/corrections are necessary, the Minutes will be amended and presented at the following IRB meeting.

The IRB reviews all submissions for initial and continuing review, as well as requests for modifications. The Primary and Secondary Reviewer present an overview of the research and lead the IRB through the completion of the regulatory criteria for approval in the "Institutional Review Board - Protocol Review/Initial Review" checklists. All members present at a convened meeting have full voting rights, except in the case of a conflict of interest (see below). In order for the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

It is the responsibility of an IRB manager to record the proceedings of the session. In addition, the IRB managers are responsible for taking Minutes at each IRB meeting.

3.5.8 Guests

The Principal Investigator will be invited to the IRB meeting to answer questions about their proposed or ongoing research. The Principal Investigator may not be present for the discussion or vote on their research.

Other guests may be permitted to attend IRB meetings at the discretion of the IRB Chair and/or the Director. Guests may not speak unless requested by the IRB and must sign a confidentiality agreement.

3.6 Criteria for IRB Approval of Research

In order for the IRB to approve human subjects research, either through expedited review or by the full IRB, it must determine that the following requirements are satisfied:

- (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.
- (5) Informed consent will be appropriately documented, in accordance with, and to the extent required by the Federal Regulations.
- (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.

These criteria must be satisfied for each review (initial, continuing and modifications) for both expedited review and review by the convened IRB.

3.6.1 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 for the research subjects, justifies asking any person to undertake the risks;
- 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 - one of the major responsibilities of the IRB - involves a series of steps:

1. **identify the risks** associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in research;
2. **determine whether the risks will be minimized** to the extent possible;
3. **identify the probable benefits** to be derived from the research;
4. **determine whether the risks are reasonable in relation to the benefits** to subjects, if any, and assess the importance of the knowledge to be gained;
5. **ensure that potential subjects will be provided with an accurate and fair description** of the risks or discomforts and the anticipated benefits;

Risks to subjects are minimized:

1. by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk; and
2. whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

Risks to subjects are reasonable in relation to anticipated benefits, if any, and to 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 (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

3.6.1.1 Scientific Merit

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;
- The research design is sound enough to reasonably expect the research to answer its proposed question; and
- The knowledge expected to result from this research is sufficiently important to justify the risk.

In making this determination, the IRB may draw on its own knowledge and disciplinary expertise, or the IRB may draw on the knowledge and disciplinary expertise of others, such as reviews by a funding agency, or departmental review. When scientific 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.

Departmental scientific review is documented by the signature of the administrative official responsible for the investigator's research unit on new protocol applications.

3.6.2 Equitable Selection of Subjects

The IRB determines by viewing the application, protocol and other research project 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.

At the time of the continuing review the IRB will determine that the PI has followed the subject selection criteria that he/she/originally set forth at the time of the initial IRB review and approval.

3.6.2.1 Recruitment of Subjects

The investigator will provide the IRB with all recruiting materials to be used in identifying participants including recruitment methods, advertisements, and payment arrangements. See Section 3.7.7 for a discussion of IRB review of advertisements, Section 3.7.8 for a discussion of IRB review of payments.

3.6.3 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 Committee 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. See Section 5 below for detailed policies on informed consent.

3.6.4 Safety Monitoring

For all research that is more than minimal risk, the investigator must submit a 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 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 determines that the safety monitoring plan makes adequate provision for monitoring the reactions of subjects and the collection of data to ensure the safety of subjects. The overall elements of the monitoring plan may vary depending on the potential risks, complexity, and nature of the research study. The method and degree of monitoring needed is related to the degree of risk involved. Monitoring may be conducted in various ways or by various individuals or groups, depending on the size and scope of the research effort. These exist on a continuum from monitoring by the principal investigator in a small, low risk study to the establishment of an independent data and safety monitoring board for a large phase III clinical trial.

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. For an individual Safety Monitor the plan must include:
 - Parameters to be assessed
 - Mechanism to assess the critical efficacy endpoints at intervals in order to determine when to continue, modify, or stop a study.
 - Frequency of monitoring
 - Procedures for reporting to the IRB
5. For a Data Safety Monitoring Board, the plan must include:
 - The name of the Data Safety Monitoring Board
 - Where appropriate, is an independent from the sponsor

- Availability of written reports
- Composition of the monitoring group (if a group is to be used): experts in all scientific disciplines needed to interpret the data and ensure patient safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease 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)

In general, it is desirable for a Data and Safety Monitoring Board (DSMB) 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 as a condition for approval of research where it determines that such monitoring is needed. When DSMBs are utilized, IRBs conducting continuing review of research may rely on a current statement from the DSMB indicating that it has and will continue to review study-wide AEs, 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. After the Board has determined whether a Data Safety Monitoring Plan is required for a given sponsored research project, the Office of Sponsored Programs will be contacted with this information and the timelines involved.

3.6.5 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**.

Definitions

Privacy - having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others.

Confidentiality - methods used to ensure that information obtained by researchers about their subjects is not improperly divulged.

Private information - 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 – information where the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

Privacy

The IRB must determine whether the activities in the research constitute an invasion of privacy. In order to make that determination, the IRB must obtain information regarding how the investigators are getting access to 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 should be 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
5. Information that is obtained about individuals other than the "target participants," and whether such individuals meet the regulatory definition of "human participant" (e.g., a subject provides information about a family member for a survey)
6. How to access the minimum amount of information necessary to complete the study.

Confidentiality

Confidentiality and anonymity are not the same. If anyone, including the investigator, can readily ascertain the identity of the subjects from the data, then the research is not anonymous and the IRB must determine if appropriate protections are in place to minimize the likelihood that the information will be inappropriately divulged. The level of confidentiality protections should be commensurate with the potential of harm from inappropriate disclosure.

At the time of initial review, the IRB ensures that the privacy and confidentiality of research subjects is protected. The IRB assesses whether there are adequate provisions to protect subject privacy and maintain confidentiality. The IRB does this through the evaluation of the methods used to obtain information:

- a. About subjects,
- b. About individuals who may be recruited to participate in studies
- c. The use of personally identifiable records and
- d. The methods to protect the confidentiality of research data.

The PI will provide the information regarding the privacy and confidentiality of research subjects at the time of initial review through the completion of the application, any necessary HIPAA Forms, research protocol, and/or other submitted, applicable materials. The IRB will review all information received from the PI and determine whether or not the privacy and confidentiality of research subjects 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 17.1).

In reviewing confidentiality protections, the IRB shall consider the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It shall evaluate the effectiveness of proposed de-

identification techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

3.6.6 Vulnerable Populations

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 6.

3.7 Additional Considerations during IRB Review and Approval of Research

3.7.1 Determination of Risk

At the time of initial and continuing review, the IRB will make a determination regarding the risks associated with the research protocols. Risks associated with the research will be classified as either "minimal" or "greater than minimal". The meeting minutes will reflect the Committee's determination regarding risk levels.

3.7.2 Period of Approval

At the time of initial review and at continuing review, the IRB will make a determination regarding the frequency of review of the research protocols. All protocols 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. biannually, quarterly, or after accrual of a specific number of participants) may be required (see below). The meeting minutes will reflect the IRB's determination regarding review frequency.

3.7.2.1 Review More Often Than Annually

Unless specifically waived by the IRB, research that meets any of the following criteria will require review more often than annually:

1. Significant risk to research subjects (e.g., death, permanent or long lasting disability or morbidity, severe toxicity) without the possibility of direct benefit to the subjects;
2. The involvement of especially vulnerable populations likely to be subject to coercion (e.g., terminally ill)
3. A history of serious or continuing non-compliance on the part of the PI.

The following factors will also 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 condition of the proposed subjects.

3. The overall qualifications of the PI and other members of the research team.
4. The specific experience of the Responsible 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 more likely.
7. 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.

3.7.3 Independent Verification That No Material Changes Have Occurred

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB verify independently, utilizing sources other than the investigator that no material changes occurred during the IRB-designated approval period. Independent verification from sources other than the investigator may be necessary at times, for example, in cooperative studies, or other multi-center research.

The IRB will determine the need for verification from outside sources on a case-by-case basis and according to the following criteria:

1. Protocols where concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources.
2. Protocols conducted by Principal Investigators who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB.
3. Protocols subject to internal audit.
4. Whenever else the IRB deems verification from outside sources is relevant.

The following factors will also be considered when determining which studies require independent verification:

1. The probability and magnitude of anticipated risks to subjects.
2. The likely medical condition of the proposed subjects.
3. The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.

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 retrospectively require such verification at the time of continuing review, review of amendments 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.

3.7.4 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 (consent monitor) is required in order to reduce the possibility of coercion and undue influence.

Such monitoring may be particularly warranted where the research presents significant risks to subjects, or if subjects are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

See Section 5.7 for a detailed discussion of consent monitoring.

3.7.5 Investigator Conflicts of Interest

The research application asks protocol-specific questions regarding conflict of interest for the investigators and key personnel. As part of its review process, the IRB will make a determination as to whether a conflict of interest exists with regard to the research under review. If a conflict of interest exists, final IRB approval of a protocol cannot be given until an approved conflict management plan that adequately protects the human subjects in the protocol is in place. (See Section 14 for a detailed discussion of Conflict of Interest)

3.7.6 Significant New Findings

During the course of research, significant new knowledge or findings about the medication or test article and/or the condition under study may develop. The PI 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. Since 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 PI contact the currently enrolled subjects to inform them of the new information. The IRB will communicate this to the PI. The informed consent should be updated and the IRB may require that the currently enrolled subjects be re-consented, acknowledging receipt of this new information and for affirming their continued participation.

If additional information affecting participant safety is submitted on a closed sponsored protocol, the IRB must be notified immediately. The information should be attached to the study and a letter sent to the IRB with the information.

The convened IRB will review the information and determine if the PI should contact subjects to inform them of the new information. The IRB will communicate this to the PI. If a letter is required, the PI will need to submit the letter for IRB review.

3.7.7 Advertisements

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

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

This information should be submitted to the IRB with the initial application or as an amendment to the protocol.

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 which 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 protocol.
2. Claims, either explicitly or implicitly, that the drug, biologic or device was 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. Claims, either explicitly or implicitly, about the drug, biologic, or device under investigation that are consistent with FDA labeling.
5. Using terms like “new treatment,” “new medication,” or “new drug” without explaining that the test article was investigational.
6. Promising “free medical treatment” when the intent was only to say participants will not be charged for taking part in the investigation.
7. Emphasis on payment or the amount to be paid, such as bold type or larger font on printed media.
8. The inclusion of exculpatory language.

Any advertisement to recruit subjects 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 clinical 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 of health exam).
8. Advertisements will not include compensation for participation in a trial offered by a sponsor to involve a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

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

3.7.8 Payment 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 coercion of subjects. Payments should reflect the degree of risk, inconvenience, or discomfort associated with participation. The amount of compensation must be proportional to the risks and inconveniences posed by participation in the study.

Investigators who wish to pay research subjects must indicate in their research project application the justification for such payment. Such justification should:

- a) Substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject;
- b) State the terms of the subject participation agreement and the amount of payment in the informed consent form; and
- c). Substantiate that subject payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue pressure on the veteran patient to volunteer for the research study.

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

Credit for payment should accrue 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 becomes coercive.

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

Unless the study is confidential, the WVU Purchasing, Contracts, and Payment Services 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 and verification of U.S. Citizenship or Permanent Resident Status to receive payment. For confidential studies only name and address are required by OBFS, but the PI MUST keep an identity key in a secure place.

At the **LAJVAMC**, payment may be permitted, with IRB approval, in the following circumstances:

1. **No Direct Subject Benefit.** When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice in affiliated non-VA institutions is to pay subjects in this situation.
2. **Others Being Paid.** In multi-institutional studies, when human subjects at a collaborating non-VA institution are to be paid for the same participation in the same study at the same rate proposed.
3. **Comparable Situations.** In other comparable situations in which, in the opinion of the IRB, payment of subjects is appropriate.
4. **Transportation Expenses.** When transportation expenses are incurred by the subject that would not be incurred in the normal course of receiving treatment and which are not reimbursed by any other mechanism.

3.7.9 Compliance with all Applicable State and Local Laws

The IRB follows and must adhere to all applicable state and local laws in the jurisdictions where the research is taking place. The HRPP and the IRB rely on the WVU General Counsel for the interpretation and application of West Virginia State law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research.

All consent forms must be consistent with applicable state and local laws.

3.7.10 Deception

Definition: Deception occurs as the result of investigators providing false or incomplete information to participants.

The IRB accepts the need for certain types of behavioral and social science studies to employ strategies that include deception. Employment of such strategies must, however, be justified. In general, deception is not acceptable if, in the judgment of the IRB, the participant may have declined to participate had they been informed of the true purpose of the research. Studies that use deception as part of their experimental design must meet all the requirements of 45 CFR §46.116(d), described below, and include a post-study debriefing, unless an exception is granted by the IRB. If such an exception is requested, this will require full board review.

In the event that a study includes the use of deception, the investigator must:

- Provide a justification for the deception (i.e., why the study could not be conducted without deception);
- Describe the manner of deception (e.g., the participants are not informed of the true intent of the study) and/or how the deception will take place (e.g., a confederate will simulate an accident);
- Note whether the deception results in any increased risk to participants (e.g., confederates engage in a staged altercation, which could result in emotional upset) *or may affect subject's willingness to participate in research*;
- Describe how any additional risks would be minimized; and
- Offer the participant the option to withdraw their data from the study in the debriefing script.

3.7.11 WVU Specimen Bank Policy

For purposes of this policy, the term, "tissue" includes any cell tissue, fluid, or excreta from which measures of normal or pathologic human physiologic function can be obtained. The term, "tissue" includes, but is not limited to pathological specimens, diagnostic specimens, hair and nail clippings, deciduous and permanent teeth, dental plaque and calculus, sweat, uncannulated saliva, placenta removed at delivery, amniotic fluid, cerebrospinal fluid, genetic material, urine, blood and other bodily fluids. First trimester fetal tissue may include additional guidelines.

a. Policy

Research using human tissue can be conducted, using the normal established guidelines for IRB review, as long as all tissue collected is either used for the purposes of the study described or discarded. If any tissue collected as part of an approved protocol, normal operating room procedure, or from a non-university affiliated institution will be banked for future research investigations at West Virginia University or its affiliates, the investigator must first register the tissue bank and then conform to the guidelines set forth in this policy for tissue banking. The policy is not directed at tissue banks that exist for other than research purposes, e.g., quality improvement or state reporting.

b. Registration

Individuals intending to create an on-site database or tissue bank utilizing clinical health information or authorized tissue specimens must complete and submit to the IRB office an "Application to Establish an On-site WVU Tissue Bank for Research or Database Development Involving Specimens Stored with or without Clinical Health Information" to register with the WVU Office of Integrity and Research Compliance. The form can be found on the IRB Forms & Samples page at http://oric.research.wvu.edu/human_subjects_research_and_the_irb/irb_forms_samples

, and is listed as the Tissue Bank Development Form. Review and formal approval for the On-site WVU Tissue Bank application will be given by the ORIC Director and one of the IRB Chairs or Vice-Chairs. Once approved the form should be submitted as part of an IRB application.

Individuals intending to create an on-site database or tissue bank utilizing clinical health information or authorized tissue specimens from decedents must still register the bank with the IRB utilizing the aforementioned form. It is expected that proper informed consent from family members to have the decedent's tissue stored will be obtained and submitted with the registration application.

c. Approval of Tissue Banking Protocols

Placement: Collection and placement of human tissue into a bank for research purposes can occur after completion and approval of an IRB protocol application. To establish an on-site Tissue Bank the approved Tissue Bank Development Form must be attached to the IRB protocol application. Human tissue, accompanied by a copy of an approved consent agreement signed by the donor, can be placed into an approved tissue bank for unspecified research purposes. Human tissue can be deposited as part of an IRB approved protocol: (1) following standard operating or delivery room procedures, (2) following standard diagnostic and treatment procedures (e.g., dental extraction, collection of bodily fluids), and (3) from a non-affiliated institution that conforms to comparable standards for the protection of human subjects. An approved protocol is needed if human tissue is to be placed into a bank as part of an approved protocol for unspecified research purposes other than that outlined in that protocol, a separate consent form obtaining approval of the donor must be obtained.

- a) Surgical Consent Form. If human tissue obtained through standard operating or delivery room (non-research) procedures is to be placed into a bank for potential research purposes, a separate consent form obtaining approval of the donor must be obtained in addition to the standard operating room consent form.
- b) Non-Surgical Consent Form. If tissue obtained for purposes of standard medical or dental diagnostic and treatment (non-research) procedures is to be placed into a bank for potential research purposes, a separate consent form must be approved by the IRB for this purpose. For example, if a blood sample is obtained for standard clinical diagnostic purposes and then discarded without identifiers, no consent is required, unless the blood is analyzed as part of a research project prior to being discarded, in which case a standard approved consent form is required. If the remaining blood or components of blood from a standard clinical diagnostic test are banked for potential research use, a signed approved consent

is required. Additionally, if the bank is on-site then the bank must be registered with the WVU Office of Research Integrity and Compliance.

- c) Tissue Acquired from a Nonaffiliated Institution. If identifiable human tissue is acquired from an institution, laboratory, or company not affiliated with West Virginia University for the purpose of tissue banking for research, the tissue must be accompanied by an approved consent agreement signed by the tissue donor. The approved consent agreement must contain comparable language to the approved WVU tissue banking language, providing assurance that the tissue can be used without additional consent as long as donor confidentiality is maintained, that tissue can be used with subject identification with additional consent, and that financial considerations regarding the cost and potential financial advantage to institutions are enumerated. If CORE (Center for Organ Recovery and Education) is involved, their consent form may be substituted.

Removal: Removal of human tissue from a bank for research purposes.

Human tissue can be removed from an approved tissue bank for research purposes with an approved protocol using the normal established guidelines for NHSR (Not Human Subjects Research), exempt, expedited, or quorum review. All researchers must apply singly for an IRB approval for each individual research project utilizing tissue from a Tissue Bank.

- a) NHSR. If human tissue is totally de-identified (stripped of all 18 Protected Health Information Identifiers) so that the researcher cannot trace the tissue back to the donor, then it is not human subjects' research (NHSR). The researcher must submit an NHSR application to the IRB for acknowledgement
- b) Exempt Research. If identifiable human tissue is removed from a bank for research purposes, but the researcher records the data without identifiers, the project qualifies as "exempt research."
- c) Expedited or Quorum Review. If identifiable human tissue is removed from a bank for research purposes and information is provided to the investigator in such a manner that human subjects can be or are identified, and the researcher uses the identifiers, the research project must follow the procedures for Expedited Review or Quorum Review.
- d) Tissue Sent to a Nonaffiliated Institution. If identifiable human tissue is removed from an approved bank at West Virginia University and sent to an institution, laboratory, or company not affiliated with West Virginia University for purposes of research, the investigator must conform to the IRB Guidelines for the Protection

of Human Subjects by obtaining approval through an approved protocol from their institution.

Approval of Tissue Banking

Policy: All research conducted on banked human tissue at West Virginia University must be obtained from an IRB-approved tissue bank.

Requirements: Requirements for IRB-Approved Tissue Banking.

All WVU Tissue Banks must have biosafety approval from the Institutional Biosafety Committee (IBC) before the IRB will approve the protocol.

Storage of tissue must be conducted in a manner conforming to the appropriate care and handling of biological specimens as outlined through the IBC Guidelines.

Disposal of tissue must be conducted in a manner conforming to the appropriate care and handling of biological specimens as outlined through the IBC Guidelines. This identification number assigned by the tissue bank will be the only method of linking the specimen, the Specimen Record, and the Donor Record. The Donor Record and the Specimen Record will be housed in separate files. The Specimen Record. The Specimen Record includes demographic and medical information from the patient's medical or research record which does not identify the patient. Variables like age (< 90), medical diagnosis, and laboratory values can be included in the Specimen Record. Variables like date of birth, hospital record number, or phone number cannot be included in the Specimen Record.

The Donor Record. Any information identifying the donor, including a copy of the approved consent agreement signed by the donor, shall be kept in the Donor Record.

Deposits of banked specimens must conform to the IRB-approved guidelines for conducting research on human tissue. All specimens in a tissue bank must be accompanied by a copy of the consent agreement signed by the donor.

Removal of banked specimens or portions of banked specimens must conform to the IRB guidelines for conducting research on human tissue. No tissue can be removed for research purposes without an approved IRB research protocol or IRB acknowledgement of a protocol involving de-identified samples.

All tissue deposited and/or removed from a tissue bank must be logged using a Tissue Bank Log which will include date and time of deposit or removal, specimen number, the

approved IRB protocol number, name(s) of investigators making the deposit or removal, and name of the tissue bank personnel responsible for completing the transaction.

Monitoring of IRB-Approved Tissue Banking: The IRB has the authority to suspend or terminate any or all research being conducted through a tissue bank that is not in compliance with IRB Guidelines. Tissue banks are subject to periodic audits.

Pre-Existing Specimens

Policy: The IRB acknowledges that there may be specimens that were collected prior to the development and enforcement of the approved policy for conducting research on human tissue, and that records accompanying these specimens may not be in compliance with these IRB Guidelines. Whenever possible, it is the duty of the tissue bank to bring records from pre-existing specimens into compliance with IRB Guidelines (e.g., obtaining copies of consent forms to accompany specimens, separating the Specimen Record from the Donor Record, completing a Tissue Bank Development Form to register an on-site Tissue Bank).

Grandfather Clause: All tissue deposited or removed from a tissue bank after 1 January 2011 must conform to the IRB Guidelines for Tissue Banking. Any tissue banked after 1 January 2011 must conform to the IRB Guidelines for removal of tissue from a tissue bank. As it may be impractical to obtain consent for many specimens deposited before 1 January 2011, the tissue bank will not be required to demonstrate evidence of informed consent for specimens collected prior to this date.

3.7.12 IRB Policy for Incidental Medical Findings during Research Studies

An incidental finding (IF) is an unexpected finding concerning an individual research participant that has potential health or reproductive importance discovered in the course of conducting research, but that is beyond the aims of the study. IFs are an increasingly common byproduct of research using powerful technologies that generate "extra" data, particularly in imaging studies and genetic studies.

Since it is not the purpose of the research to look for incidental findings, the researcher may not be capable of verifying that a potential IF is clinically important. In the case of imaging studies, the parameters of the study may not be optimal for detecting or verifying potential lesions. Before a subject is informed about an IF, it is necessary that the investigator clearly establish whether the IF is medically important. In order to accomplish this, it may be necessary to consult with a radiologist in the case of imaging studies. In the case of a genetic IF, verification from a genetics laboratory approved to perform clinical tests under the Clinical Laboratory Improvements Amendments (CLIA) may be required.

There are specific research areas that have reported high rates of incidental findings. Among these are genetic family studies where genetic variants may be identified that may cause or increase susceptibility to phenotypic disease or disability, or where misattributed paternity or other misattributed lineage may be discovered by the researchers. Another area would be MRI studies of the brain or elsewhere in the body where masses, various anatomical malformations, evidence of cranial bleed or stroke, evidence of infection, evidence of injury, and evidence of dementia may be discovered. An area of increasing IFs is that of CT colonography research where anatomical malformations, masses, aneurisms, evidence of infection, and evidence of injury or trauma may be seen.

Reanalysis of archived data is an overlooked source of IFs. Archived data may consist of genetic data or imaging data that may yield the evidence of IFs, when reevaluated in the future. In some cases, archived data is truly anonymous and the subject cannot be identified. In other cases, however, the identity of the subject can be ascertained, and the subject may be contacted, if necessary. If the IFs are such that potential clinical benefits to subjects are likely, all reasonable effort should be made to contact subjects.

These are not the only sources of incidental findings. Social and behavioral research may reveal evidence of alcoholism, drug abuse, mistreatment, or mental illness when these are not the objectives of the study. In many cases, if these findings are discovered, the investigator must report the evidence to local authorities.

In summary, any type of research may reveal incidental findings that might or might not affect the health and welfare of the potential subject and must, therefore, be considered by the investigator and the IRB. Since this is the case, the policy for West Virginia University must be broad enough to cover most of the possibilities, but not be so cumbersome as to be totally useless.

The first question that must be asked is: Should all incidental findings be discussed with the subjects? Although some institutions take this stance, it appears that most do not. . Because the disclosure of IFs can potentially save lives but also cause alarm and other potential harm, the decision on whether or not to disclose them to research participants constitutes a major dilemma. Researchers often stumble upon unexpected findings but have no idea whether to share this information with research participants. The information may prove highly significant or a false alarm. Current best practice distinguishes among three categories of IFs to determine if and when they should be disclosed.

- IFs with strong net benefits—ones revealing a condition likely to be life-threatening or revealing a condition likely to be grave that can be avoided—should be offered to research participants as soon as practical.
- An IF that offers possible net benefit—one that may offer more benefit than burden to the research participant—may be disclosed at the researcher's discretion.

- An IF that has unlikely net benefit or whose net benefit cannot be determined should not be offered to the research participant, because disclosure may well present more burden than benefit.

In the case of an IF with suspected or known strong net benefits, the following should be followed prior to the subject leaving the facility. If the IF involves a medical condition and if the researcher is not a clinician or qualified to interpret the IF, a knowledgeable physician should be contacted immediately to review the finding to determine the likelihood of net benefit. The subject should be informed by the investigator (if he/she is qualified) or by the physician that was contacted of the nature of the finding. If warranted and the subject agrees, the contacted physician should directly examine the subject. The subject should be informed that any medical information found will be sent to his/her personal physician (unless the subject objects). If the subject indicates that he/she does not wish to be informed of the incidental findings, even if it is high health importance and utility, and such findings are discovered, additional considerations may be warranted. It is the policy of WVU that, without revealing the information, the researcher should attempt to confirm that the research participant indeed wants to refuse even information that may have "life or death" consequences to him/her. If the participant indicates that he/she does not wish to be informed, the wishes of the participant should be honored. If this occurs, a notation should be made a permanent part of the participant's research record and should also be transmitted to the IRB in a timely fashion.

The notification of the personal physician is the extent of West Virginia University's responsibility in the matter.

If the IF is one in which possible net benefit to the subject, the investigator should consult with an appropriate clinician if the investigator does not possess the necessary expertise. If it is decided that the subject should be informed, this should be accomplished as soon as practical and any medical information should be sent to his/her personal physician (again unless the subject objects). The subject should be directly informed about any non-medical information.

The researcher should send a letter detailing the procedure followed to the Principal Investigator of the study with a copy being sent to the Office of Research Compliance.

The policy of informing (or not informing) potential subjects in the event of IFs should be included in all informed consent documents in which Ifs are a possibility.

(It is recommended that a specific policy, based on the above general rules be created for separate units)

3.8 Possible IRB Actions

Approval - the study is approved as submitted.

Board Modification- the protocol and/or consent form require minor revisions, such as wording changes, with replacement language provided. For protocols reviewed at a convened IRB meeting, the needed revisions are agreed upon at the IRB meeting. For protocols reviewed under expedited review, the needed revisions are designated by the reviewer(s). None of the required modifications can be related to the regulatory criteria for approval. These revisions are presented to the PI for incorporation by simple concurrence. Revisions must be made exactly as designated by the IRB or reviewer(s).

In order to receive approval for a protocol deferred for non-substantive issues:

- For full review, the investigator's response, the revised protocol and the previously submitted protocol is given to the IRB Chair, Vice Chair, or a subcommittee of the IRB for review. The reviewer(s) may approve the study upon receipt and approval of the revisions without further action by the IRB.
- For expedited, the investigator's response, the revised protocol and the previously submitted protocol is given to the same reviewer(s) for re-review or to a subcommittee.

Approval of the protocol application will not be granted and certification will not be issued until all deficiencies, if any, are corrected to the satisfaction of the IRB or the reviewer(s).

The outcome of the IRB's deliberations is once again communicated to the investigator in writing.

The IRB's determination concerning the subsequent amended submission will be documented in the minutes of the next IRB meeting or in the file for expedited review.

Note: For full review, the expiration date for the protocol is calculated based on the date of the last convened IRB meeting and NOT on the final approval date.

Deferred for substantive issues regarding the protocol and/or consent form that must be addressed. This action is taken if substantial modification or clarification is required, or insufficient information is provided to judge the protocol application adequately (e.g., the risks and benefits cannot be assessed with the information provided). IRB approval of the proposed research must not occur until subsequent review of the material the PI submitted by the convened IRB or the expedited reviewer(s).

In order to receive approval for a protocol deferred for substantive issues:

- For full review, the investigator's response must be submitted for review at a subsequent, convened meeting of the same IRB. The ORIC provides the IRB with the investigator's response, the revised protocol and the previously submitted protocol. The item is placed on the agenda for re-review at the next meeting.
- For expedited, the investigator's response, the revised protocol and the previously submitted protocol is given to the same reviewer(s) for re-review.

Approval of the protocol application will not be granted and certification will not be issued until all deficiencies, if any, are corrected to the satisfaction of the IRB or the reviewer(s).

The outcome of the IRB's deliberations is communicated to the investigator in writing.

The IRB's determination concerning the subsequent amended submission will be documented in the minutes of the IRB meeting or in the file for expedited review.

Note: Failure to submit a response to IRB-stipulated changes or inquiries related to deferred protocols within 75 days of the IRB date of determination will result in administrative closure of the IRB file. The PI will receive notification of the closure of the IRB file, including an explanation for this action. An extension beyond 75 days may be granted by the IRB if sufficient cause is provided by the PI.

Disapproved. The IRB has determined that the research cannot be conducted at WVU or by employees or agents of WVU or otherwise under the auspices of WVU.

Approval in Principle. As per federal regulations, (45CFR46.118), there are two circumstances in which the IRB may grant approval required by a sponsoring agency without having reviewed all of the study procedures and consent documents. One is if study procedures are to be developed during the course of the research, but human subjects approval is required by the sponsoring agency. The other is if the involvement of human subjects depends on the outcomes of work with animal subjects. The IRB may then grant approval without having reviewed the as yet undeveloped recruitment, consent, and intervention materials. However, if the proposal is funded, the Principal 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. Approval in principle is granted to satisfy sponsoring agency requirements or to allow investigators to have access to funding to begin aspects of the project that do not involve human subjects.

3.9 Study Suspension, Termination and Investigator Hold

3.9.1 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 8 for a discussion of unexpected problems and Section 10 for a discussion of non-compliance)

Suspension of IRB approval is a directive of the convened IRB or IRB Chair or the Director to temporarily stop some or all previously approved research activities short of permanently stopping all previously approved research activities. Suspension directives made by the IRB Chair or Director must be reported to a meeting of the convened IRB. Suspended protocols remain open and require continuing review.

Termination of IRB approval is a directive of the convened IRB to stop permanently all activities in a previously approved research protocol. Terminated protocols are

considered closed and no longer require continuing review. Terminations of protocols approved under expedited review must be made by the convened IRB.

The IRB shall notify the PI in writing of such suspensions or terminations and shall include a statement of the reasons for the IRB's actions. The terms and conditions of the suspension must be explicit. The investigator shall be provided with an opportunity to respond in person or in writing.

When study approval is suspended or terminated by the convened IRB or an authorized individual, in addition to stopping all research activities, the convened IRB or individual ordering the suspension or termination will notify any subjects currently participating that the study has been suspended or terminated. The convened IRB or individual ordering the suspension or termination will consider whether procedures for withdrawal of enrolled subjects are necessary to protect their rights and welfare of subjects, such as: transferring participants to another investigator; making arrangements for care or follow-up outside the research; allowing continuation of some research activities under the supervision of an independent monitor; or requiring or permitting follow-up of participants for safety reasons.

If follow-up of subjects for safety reasons is permitted/required by the convened IRB or individual ordering the suspension or termination, the convened IRB or individual ordering the suspension or termination will require that the subjects should be so informed and that any adverse events/outcomes be reported to the IRB and the sponsor.

Investigator **MUST** continue to provide reports on adverse events and unanticipated problems to both the IRB and sponsor 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.)

Note: Suspension or termination of protocols approved by the IRB can also be issued by WVU officials acting outside of and unrelated to the HRPP (i.e., not necessarily related to protecting the rights and welfare of study participants). Such University actions can be made by the University President, Provost, and Deans. Such University actions may be made for any reason in furtherance of the Institution's interest provided, however, that the aggrieved PI is entitled to all rights and procedures afforded to him/her under the Grievance Policy. The PI must report any suspension or termination of the conduct of research by organization officials to the IRB. The IRB will then determine if suspension or termination of IRB approval is warranted.

3.9.2 Investigator Hold

An investigator may request an administrative hold on a protocol when the investigator wishes to temporarily or permanently stop some or all approved research activities. An administrative hold is initiated by an investigator. Administrative holds are not suspensions or terminations.

3.9.2.1 Procedures

1. Investigators must notify the IRB in writing that:

- a. They are voluntarily placing a study on administrative 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 harm
2. Upon receipt of written notification of the investigator an IRB Manager places the research on the agenda for review.
 3. The IRB Chair and/or Director, in consultation with the investigators, determine 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” below.
 4. The IRB Chair and/or Director, in consultation with the investigators, determine how and when currently enrolled participants will be notified of the administrative hold.
 5. Investigators may request a modification of the administrative hold by submitting a request for a modification to previously approved research.

3.9.3 Protection of Currently Enrolled Participants

Before an administrative hold, termination, or suspension, is put into effect the convened IRB or IRB designee 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
- 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

3.10 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 protocol, but not less than once per year. Continuing review must occur as long as the research remains active for long-term follow-up of participants, even when the research is permanently closed to the enrollment of new participants and all participants have completed all research-related interventions. Continuing review of research must occur even when the remaining research activities are limited to the analysis of private identifiable information.

3.10.1 Approval Period

At WVU, determination of the approval period and the need for additional supervision and/or participation is made by the IRB on a protocol-by-protocol basis. For example, for an investigator who is performing particularly risky research, or for an investigator who has recently had a protocol suspended by the IRB due to regulatory concerns, an on-site review by a subcommittee of the IRB might occur or approval might be subject to an audit of study performance after a few months of enrollment, or after enrollment of the first several subjects.

For each initial or continuing approval the IRB will indicate an approval period with an approval expiration date specified. IRB approval is considered to have lapsed at midnight on the expiration date of the approval. For a study approved by the convened IRB, the approval period starts on the date that the IRB conducts its final review of the study; that is, the date that the convened IRB or subcommittee approved the research or the date the convened IRB deferred the research for non-substantive issues. For a study approved under expedited review, the approval period begins on the date the IRB Chair or IRB member(s) designated by the Chair gives final approval to the protocol.

The approval date and approval expiration date are clearly noted on all IRB certifications sent to the PI and must be strictly adhered to. Investigators should allow sufficient time for development and review of renewal submissions.

Review of a change in a protocol ordinarily does not alter the date by which continuing review must occur. This is because continuing review is review of the full protocol, 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.

3.10.2 Continuing Review Process

To assist investigators the ORIC staff will send out renewal notices to investigators three months, two months and 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:

1. the initial review application updated with any changes;
2. the current consent document;
3. any newly proposed consent document; and
4. the protocol renewal form.

In conducting continuing review of research not eligible for expedited review, all IRB members are provided and review all of the above material and the Primary Reviewer will review the complete protocol, including any modifications previously approved by the IRB. At the meeting, the Primary and Secondary Reviewers lead the IRB through the completion of the regulatory criteria for approval in the “Institutional Review Board - Protocol Review/Continuing Review” checklists.

HRPP staff attend the convened meetings and have completed protocols available. The IRB staff will retrieve any additional related materials the IRB members request.

In the case of expedited review, the IRB members may request the HRPP staff to provide them with any additional materials required for the review.

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

3.10.3 Expedited Review of Continuing Review

In conducting continuing review under expedited review, the reviewers receive all of the above material. The reviewer(s) complete the “Institutional Review Board - Protocol Review/Continuing Review” checklists 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) at 63 FR 60364-60367 (see Expedited Review Categories). It is also possible that research activities that previously qualified for expedited review in accordance with 45 CFR 46.110, have changed or will change, such that expedited IRB review would no longer be permitted for continuing review.

3.10.4 What Occurs if There is a Lapse 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 the continuing review does not occur within the timeframe set by the IRB, all research activities must stop, including recruitment (media advertisements must be pulled), enrollment, consent, interventions, interactions, and data collection, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. **This will occur even if the investigator has provided the continuing information before the expiration date. Therefore, investigators must allow sufficient time for IRB review before the expiration date.**

The ORIC is responsible for immediately notifying the investigator of the expiration of approval and that all research activities must stop. (Note: Notifications are generated and delivered electronically.)

If research participants are currently enrolled in the research project and their participation is ongoing, once notified of the expiration of approval the PI must immediately submit to the IRB Chair a list of research subjects for whom suspension of the research would cause harm. Enrollment of new subjects cannot occur and continuation of research interventions or interactions for already enrolled subjects should only continue when the IRB or IRB Chair finds that it is in the best interest of the individual subjects to do so.

For VA research

The Director and IRB Chair, with appropriate consultation with the LAJVAMC Chief of Staff (COS), determine if the subject may continue in the research.

Failure to submit continuing review information on time is non-compliance and will be handled according to the non-compliance policy (See Section 10.3).

Once approval has expired, IRB review and re-approval must occur prior to re-initiation of the research. If the study approval has lapsed more than 30 days and the PI has not provided the required continuing review information, the PI must submit a new application to the IRB for review and approval. If the study approval has lapsed 30 days or less and the PI provides the required continuing review information, the existing protocol may be reviewed for consideration of continued IRB approval.

If a research protocol receives contingent approval at the time of the continuing review and the approval expires before the PI responds to the contingencies, the PI may not enroll any new subjects or access medical records after the approval expiration date. Once the PI responds, the existing protocol will be reviewed for continuation. If the PI does not respond for an extended period, the IRB may vote to administratively close the study. Decisions of this kind must be made in a manner that ensures that closure will not harm any participants previously enrolled who may require ongoing treatment as part of the research study.

3.11 Amendment of an Approved Protocol

Investigators may wish to modify or amend their approved applications. **Investigators must seek IRB approval before making any changes 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 hazard to the subject (in which case the IRB must then be notified at once).

Modifications may be approved if they are within the scope of what the IRB originally authorized. For example, if a researcher wishes to add a population to an existing study, but not alter the study procedures or purpose, a modification request is usually appropriate. Likewise, modifying a procedure without changing the study's purpose or study population may also be appropriate. If, however, the researcher wishes to add a population and revise study procedures, he or she will need to submit a new application for human subjects approval.

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

- Completed “Request for Protocol Amendment” form;
- Revised Investigator’s protocol application or sponsor’s protocol (if applicable)
- Revised approved consent/parental permission/assent documents (if applicable) or other documentation that would be provided to subjects when such information might relate to their willingness to continue to participate in the study
- Revised or additional recruitment materials
- Any other relevant documents provided by the investigator

ORIC staff will determine whether the proposed changes may be approved through an expedited review process, if the changes are minor, or whether the modification warrants full 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 protocol for full board review.

3.11.1 If an amendment for VA research addresses an issue related to biosafety or radiation safety, the appropriate committee or subcommittee first approves the amendment, when appropriate. Expedited review of Protocol 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 designee(s) among the IRB members.

The reviewer(s) complete the “Reviewer” checklists to determine whether the modifications meet the criteria allowing review of the amendment 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 participants’ willingness to continue to take part in the research and if so, whether to provide that information to participants.

3.11.2 Full Board Review of Protocol Modifications

When a proposed change in a research study is not minor (e.g., procedures involving increased risk or discomfort are to be added), 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 receive and review all documents provided by the investigator.

At the meeting, the Primary Reviewer presents an overview of the modifications and leads the IRB through the completion of the regulatory criteria for approval. The IRB will 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 participants.

3.12 Closure of Protocols

The completion or termination of the study, whether premature or not, 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.

Investigators may submit closure applications to the IRB on a closure report.

The completion of a sponsored protocol will have a reminder in the closure acceptance letter stating the following: Please be aware that if the sponsor contacts you with any information directly affecting participant safety, you must submit this information to the IRB regardless of the status of the study. A notification should be sent to the Office of Research Integrity and Compliance and the full report should be added to the study. (Please use the electronic notepad for studies in BRAAN.)

3.13 Flagging Of the VA Medical Record

For VA research, the IRB determines whether the medical record has to be flagged to protect the participant's safety by indicating participation in the study and the source of more information on the study. This should be a systematic determination for each protocol. The IRB cannot delegate this requirement back to the VA.

The IRB may not want to require the medical record to be flagged or may consider lifting the flagging requirement if:

1. The subject's participation in the study involves:
 - a. Only one encounter,
 - b. Only the use of a questionnaire, or
 - c. The use of previously collected biological specimens.
2. The identification of the patient as a subject in a particular study (if the study is not greater than minimal risk) would place the subject at greater than minimal risk.

3.14 Reporting IRB Actions

All IRB actions are communicated to the Principal Investigator (RPI), or designated primary contact person for the protocol, in writing usually within ten (10) working days via a template letter prepared by the IRB staff and signed by the IRB Chair or designee. For an approval, along with written notification of approval, a copy of the approved consent form containing the stamped approval with the dates of the approval and expiration on each sheet will be sent to the investigator. For a deferral or board modifications, the notification will include the modifications required for approval 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 should be copied to the chair of the appropriate department.

All letters to investigators must be filed in the protocol files maintained by the IRB

The IRB reports its findings and actions to the institution in the form of its minutes, which are distributed by IRB staff to the WVU Institutional official and are stored permanently and securely in the ORIC.

The LAJVAMC has additional approval requirements relating to the R&D committee. All protocol reviews by WVU IRB cannot be implemented until R&D approval has been obtained. Final approval documents and stamped, dated consent forms are sent to the investigator and WVU HRPP by the VA Research Office.

3.15 Appeal of IRB Decisions

When an IRB protocol presented at a convened meeting is disapproved or deferred, the IRB will notify the PI 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. If an investigator disagrees with any Board decisions or action, he or she may request reconsideration by either appearing before the Board or by requesting an advisory review panel. This request must be made to the Office of Research Integrity and Compliance, in writing, within seven calendar days of the investigator's receipt of the Board's notification

3.15.1 Procedure

The entire appeal process must be completed within 120 calendar days of the investigator's receipt of the Board's notification to suspend or terminate study.

The Decision of the Board becomes final under any of the following circumstances:

- The Investigator chooses not to appeal.
- The investigator fails to notify the Office of Research Integrity and compliance within seven calendar days of receipt of the Board's notification, of a decision to appeal.

- The investigator or a representative fails to appear before the Board at its next regularly scheduled meeting.
 - The investigator fails to request formation of an advisory review panel within seven calendar days after appearing before the Board.
 - The investigator fails to make documents concerning the study available to the advisory review panel within seven calendar days of being requested to do so.
 - Final Decisions by Board after receipt of Appeal Committee recommendation.
- The Board will notify all appropriate parties.

3.15.2 Investigator Appears Before the Board

An investigatory may ask to appear before the Board to request that the Board reconsider a decision; this appearance **must** be at the next regularly scheduled IRB meeting. The Board may affirm, modify, or reverse its original decision. Within seven calendar days, the Board will notify the investigator of its decision. If the investigator is still dissatisfied, he or she may now have seven calendar days to request (In writing to the Office of Research Integrity and Compliance) formation of an advisory panel review.

3.15.3 Advisory Review Panel

An Investigator may request reconsideration based on the report of an advisory review panel.

The advisory review panel must be formed within 15 calendar days of the investigator's request for its formation.

3.15.3.1 Composition

An advisory review panel shall consist of three persons:

- One member chosen by the IRB chair; this person may not be a current member of the Board or the IRB staff
- One member chosen by the principal investigator; this person may not be a member of the investigator's department and may not have had any direct involvement in the activities in question.
- One member chosen by the Institutional Official (IO); this person will serve as chair, may not be a current member of the Board or the IRB staff, may not be a member of the Board or the IRB staff, may not be a member of the investigator's department, and may not have had any direct involvement in the activities in question.

3.15.3.2 Meeting and Report

Within 30 calendar days of its formation, the panel will complete its investigation and transmit to the IRB chair a written report of its findings and recommendations. During its investigation, the panel may involve the office of the university's general

counsel. The Board will consider this report at a regular or special meeting held within 30 calendar days of the chair's receipt of the report.

The Board will provide written notice (within seven calendar days) of its decision to the appropriate investigator(s), department chair(s), members of the advisory panel, and others as deemed appropriate.

3.15.3.3 IRB Determination

The Institutional Review Board's determination whether to accept the Appeal Committee Report recommendation will constitute the final decision regarding the investigator appeal.

3.16 National Cancer Institute's Central IRB Adult and Pediatrics Initiative

WVU is a participant in the National Cancer Institute's Central Institutional Review Board (CIRB) Initiative. The WVU IRB has granted NCI-CIRB initial, amendment, and continuing reviews of Phase II/III Cooperative Group Adult Cancer treatment protocols.

An Inter-institutional Authorization Agreement (IAA) exists between WVU and the NCI-CIRB, making NCI-CIRB the IRB of record.

Obtaining Approval:

- 1) Investigators who qualify with NCI receive passwords and usernames from the NCI-CIRB to gain access to the NCI CIRB website as well as the IRB Manager for protocol submissions.
- 2) The investigators seek out NCI protocols of interest. Investigator's must then complete a Study-Specific Worksheet and be site approved by the NCI-CIRB to conduct the study. Upon NCI-CIRB's acceptance, the protocol is prepared for submission to the WVU IRB. The investigator submits the NCI approved materials with consent form to the WVU IRB for expedited review by the administrator to determine if the CIRB review is acceptable to the local IRB and will decide whether to accept the CIRB review.
- 3) The submission to the WVU IRB must contain the initial or continuing review approval letter containing the CIRB expiration date of the approved protocol, the CIRB protocol, the CIRB-approved consent form, and the WVU PRMC Approval Letter.
Note: NCI will not allow deletion of any information from the consent document. Minor word substitutions or additions to the consent form, e.g. WVU's requirements or policies, to simplify or clarify statements, as long as the changes do not alter the meaning of the CIRB-approved contents are allowed. If the expedited review finds additional risk language is necessary, the consent may be changed in consultation with the CIRB.
- 4) Modifications Required (in order to secure approval for CIRB Oversight): Specific stipulations must be addressed before the CIRB can be designated as the IRB of record.
- 5) Protocol Not Accepted (for CIRB Oversight): Local IRB oversight is required. The PI must complete a local IRB application and submit materials to ORIC via the

standard application process. The CIRB will not be permitted to oversee the protocol.

- 6) After review and approval, the PI will receive a WVU IRB approval letter.

When a Protocol has been approved for CIRB Oversight

- 1) Once the CIRB is designated as the IRB of record for a study, all consent form revisions, continuing reviews, amendments and study closures are submitted to the NCI-CIRB and are reviewed and approved by the NCI-CIRB.
- 2) Any Serious adverse events, deviations, or Unanticipated Problems Involving Risks to the Subjects or Others that occur at WVU must be submitted for evaluation in the same manner as from any other protocol utilizing the WVU IRB as the IRB of record.
- 3) Closures should be reported to the WVU-IRB.

WVU Responsibilities

- 1) WVU will ensure the safe and appropriate performance of the research at WVU and will ensure that investigators and other staff at WVU who are conducting the research are appropriately qualified and trained.
- 2) HRPP will notify the CIRB immediately if there is a suspension or restriction of a local investigator.
- 3) WVU will maintain a local IRB whose membership satisfies the requirements of 45 CFR 46 and 21 CFR 56.
- 4) Please see the Authorization Agreement/Division of Responsibilities document for additional Signatory Institution Responsibilities.

NCI CIRB Responsibilities

- 1) Maintain an NCI CIRB membership that satisfied the requirements of 45 CFR 46 and 21 CFR 56 and provides special expertise as needed to adequately assess all aspect of each study
 - a) Post the roster of NCI CIRB membership on the public side of the NCI CIRB website
- 2) Conduct initial, amendment, and continuing review of studies as well as review of any other study-specific documents submitted by the Study Chair to the NCI CIRB
- 3) Conduct review of local context consideration as outlined in the following Worksheets:
 - a) Annual Signatory Institution Worksheet About Local Context
 - b) Annual Principal Investigator Worksheet About Local Context
 - c) Study-Specific Worksheet About Local Context
- 4) Conduct review of potential unanticipated problems and/or serious or continuing noncompliance when the Signatory Institution or other entity reports an incident, experience, or outcome to the CIRB

- a) This review includes reporting any unanticipated problem and/or serious or continuing noncompliance determination to OHRP, the FDA, and the Signatory Official for the NCI.
- 5) Report any suspension or termination of CIRB approval to OHRP, FDA, and the Signatory Official for the NCI
- 6) Conduct review of individual Adverse Event Reports for study without a Data and Safety Monitoring Board (DSMB) or equivalent monitoring body
- 7) Provide institution-specific documents related to CIRB reviews to a secure website and notify research staff and institutional designees of the posting via broadcast emails
- 8) Post all study-wide documents related to CIRB reviews via email to research staff and institutional designees
- 9) Notify the Signatory Institution immediately if there is ever a suspension or restriction of the CIRB's authorization to review and study
- 10) Post the NCI CIRB Standard Operating Procedures on the public side of the CIRB website.



**Human Research Protections Program
(HRPP)**

Office of Research Integrity & Compliance

STANDARD OPERATING PROCEDURES

Section #: 4

Title: *Documentation and Records*

Date: December 10, 2010

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4 Documentation and Records

WVU shall prepare and maintain adequate documentation of the IRB's activities. All records must be 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.

4.1 IRB Records

IRB records include, but are not limited to:

1. Written operating procedures. (See Chapter 1.10)
2. IRB membership rosters, (See Chapter 4.4)
3. Training records. The IRB Administrator maintains accurate records listing research investigators, IRB members, and IRB staff that have fulfilled the facility's human subject training requirements. Electronic copies of documentation are maintained in the official IRB records located in the ORIC.
4. IRB correspondence (other than protocol related).
5. IRB Study Files (See Chapter 4.2 for information included in study files)
6. Documentation of Emergency Exemption from Prospective IRB Approval. (21 CFR 56.104(c)). See Chapter 8.6.1)
7. Documentation of Exceptions from Informed Consent Requirements for Emergency Use of a Test Article ((21 CFR 50.23). (See Chapter 7.4.3)
8. Documentation of exemptions (See Chapter 4.5)
9. Documentation of convened IRB meetings minutes (see Chapter 4.3 for information included in the minutes).
10. Documentation of review by another institution's IRB when appropriate.
11. Documentation of IRB Authorization Agreements (IAA)
12. Federal Wide Assurances.
13. Protocol violations submitted to the IRB

14. Quality assurance reviews.

4.2 IRB Study Files

The IRB will maintain a separate IRB study file for each research application (protocol) that it receives for review. Protocols will be assigned a unique identification number by the electronic system and entered into the IRB tracking system.

Accurate records are maintained of all communications to and from the IRB. Copies are filed in the Principal Investigator's project file. The WVU IRB maintains a separate file for each research protocol that includes, but is not limited to:

1. Protocol and all other documents submitted as part of a new protocol application.
2. Protocol and all other documents submitted as part of a request for continuing review/termination of research application. This also includes progress reports, statements of significant new findings provided to participants, reports of injuries to patients.
3. Documents submitted and reviewed after the study has been approved, including reports of modifications to research/amendments and adverse event reports.
4. Copy of IRB-approved Consent Form
5. DHHS-approved sample consent form document and protocol, when they exist
6. IRB reviewer forms (when expedited review procedures are used) and scientific reviewer forms (where applicable).
7. Documentation of type of IRB review.
8. For expedited review, documentation of any determinations required by the regulations and protocol-specific findings supporting those determinations, including: waiver or alteration of the consent process, research involving pregnant women, fetuses, and neonates, research involving prisoners, and research involving children.
9. Documentation of all IRB review actions.
10. Notification of expiration of IRB approval to the PI and instructions for submitting relevant continuing review materials.
11. Notification of suspension of research.
12. Correspondence pertaining to appeals.
13. Copies of approval letters and forms that describe what Principal Investigator must have before beginning the study.
14. IRB correspondence to and from research investigators.
15. All other IRB correspondence related to the research.
16. For devices, a report of prior investigations.
17. Reports of unanticipated problems involving risk to subjects or others and adverse events.

18. Documentation of audits, investigations, reports of external site visits.

4.3 The IRB Minutes

Proceedings must be written and available for review by the next regularly scheduled IRB meeting date or within three weeks of the meeting date, whichever comes first. Once approved by the members at a subsequent IRB meeting, the minutes must not be altered by anyone including a higher institutional authority.

A copy of IRB-approved minutes for each IRB meeting will be distributed to the IO and, for VA research, the R&D Committee.

Minutes of IRB meetings must contain sufficient detail to show:

1. Attendance
 - a. Names of members 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 only as designated on the official IRB membership roster)
 - d. Names of consultants present
 - e. Name of investigators present
 - f. Names of guests present

Note: The initial 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 those members present for the vote on that item. Members who recuse themselves because of conflict of interest are listed by name and the reason documented.

2. The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area
3. Business items discussed
4. Continuing Education
5. Actions taken, including separate deliberations, actions, and votes for each protocol undergoing initial review, continuing review, or review of modifications by the convened IRB
6. Votes on these actions (Total Number Voting; Number voting for; Number voting against; Number abstaining; Number of those excused, Number of those recused)

7. Basis or justification for these actions including required changes in research
8. Summary of controverted issues and their resolution
9. Approval period for initial and continuing approved protocols, including identification of research that warrants review more often than annually and the basis for that determination
10. Risk level of initial and continuing approved protocols
11. Review of interim reports, e.g. unanticipated problems or safety reports; amendments; report of violation/deviations; serious or continuing non-compliance; suspensions/terminations, etc.
12. Review of Data and Safety Monitoring Board (DSMB) summary (if applicable)
13. Review of Plans for Data and Safety Monitoring
14. Justification of deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document.
15. Protocol-specific documentation that the research meets the required criteria [45 CFR 46.116(d)] 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 an informed consent
16. Protocol-specific documentation that the research meets the required criteria [45 CFR 46.117(c)] when the requirements for documentation of consent are waived
17. When approving research that involves populations covered by Subparts B, C, or D of 45 CFR 46, the Minutes will document the IRB's justifications and findings regarding the determinations stated in the Subparts or the IRB's agreement with the findings and justifications as presented by the investigator on IRB forms as applicable.
18. Special protections warranted in for other groups of subjects who are likely to be vulnerable to coercion or undue influence, such as mentally disabled persons, or economically or educationally disadvantaged persons, regardless of source of support for the research.
19. The rationale for significant risk/non-significant risk device determinations.
20. Determinations of conflict of interest.
21. 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.
22. A list of research approved since the last meeting utilizing expedited review procedures.
23. The approval of research contingent on specific minor conditions by the chair or designee is documented in the minutes of the first IRB meeting that takes place after the date of the approval.

24. An indication that, when an IRB member has a conflicting interest (see Section 2.8) with the research under review, the IRB member was not present during the deliberations or voting on the proposal, and that the quorum was maintained.
25. Key information provided by consultants will be documented in the minutes or in a report provided by the consultant

4.4 IRB Membership Roster

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

1. Name
2. Earned degrees
3. Affiliated or non-affiliated status (neither the member nor an immediate family member of the member may be affiliated with the Organization)
4. Status as scientist (physician-scientist, other scientist, non-scientist or social behavioral scientist). For purposes of this roster, IRB members with research experience are designated as scientists (including the student member). Research experience includes training in research (e.g., doctoral degrees with a research-based thesis) and previous or current conduct of research. Students being trained in research fields will be designated as scientists.
5. Indications of experience, such as board certifications or licenses sufficient to describe each member's chief anticipated contributions to IRB deliberations.
6. Representative capacities of each IRB member: which IRB member is a prisoner representative (as required by Subpart C), and which IRB members are knowledgeable about or experienced in working with children, pregnant women, cognitively impaired individuals, and other vulnerable populations locally involved in research.
7. Role on the IRB (Chair, Co-Chair, etc.)
8. Voting status (Any *ex officio* members are non-voting members)
9. For alternate members, the primary member or class of members for whom the member could substitute

The ORIC must keep IRB membership list current. The Director of the ORIC must promptly report changes in IRB membership to the Office for Human Research Protections, Department of Health and Human Services.

4.5 Documentation of Exemptions

Documentation of verified exemptions consists of the reviewer's citation of a specific exemption category and written concurrence that the activity described in the investigator's request for satisfies the conditions of the cited exemption category as

detailed in Section 3.3. The exempt determination is reported at the next convened IRB meeting and documented in the Minutes.

4.6 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 under expedited review as described in Section 3.4; the approval period and any determinations required by the regulations including protocol-specific findings supporting those determinations.

4.7 Access to IRB Records

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

1. IRB records are kept in a protected electronic system. Paper copies of protocols that were closed prior to the electronic system are kept in the office. Doors to the ORICs are closed and locked when the rooms are unattended.
2. Ordinarily, access to all IRB records is limited to the Director, IRB Chair, IRB members, IRB Administrator, IRB staff, authorized institutional officials, and officials of Federal and state regulatory agencies (OHRP, FDA). Research investigators are provided reasonable access to files related to their research. Appropriate accreditation bodies are provided access and may recommend additional procedures for maintaining security of IRB records. All other access to IRB records is limited to those who have legitimate need for them, as determined by the IO and 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 ORIC; however, the IRB staff will provide copies of records for authorized personnel if requested.
5. All other access to IRB study files is prohibited.

4.8 Record Retention

IRB records (as described in Section 4.2) are retained by the facility for at least three (3) years after completion of the research. IRB records relating to VA research are retained for at least five year after completion of the research, and all other records are retained for at least five (5) years.

IRB Records pertaining to research, which is conducted, must be retained for at least three years after completion of the research. IRB records not associated with research or for protocols cancelled without participant enrollment will be retained at the facility for at least 3 years after closure. If a VA study is closed with or without participant enrollment, records should be maintained for at least five years after closure.

Records are stored in a secure electronic system and can only be accessed by the Office of Research Integrity and Compliance staff. With the adoption of an electronic web based system, all records are maintained indefinitely, but are electronic in nature. All records will be backed up and stored off-site, according to security and storage policies of West Virginia University Information Technology Office.

For VAMC research, the required records must be retained in accordance with VHA's Records Control Schedule (RCS 10-1). As part of the oversight responsibility, the VA R&D committee must have access to protocols of that VA facility.

 <p>West Virginia University Human Research Protections Program (HRPP) Office of Research Integrity & Compliance STANDARD OPERATING PROCEDURES</p>	<p>Section #: 5 Title: <i>Obtaining Informed Consent from Research Subjects</i> Date: December 10, 2010 Page: Page 93 of 194</p>
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5 Obtaining Informed Consent from Research Subjects

No investigator conducting research under the auspices of WVU may involve a human being as a subject in non-exempt 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 5.8 of these procedures. Except as provided in Section 5.9 of these procedures, informed consent must be documented by the use of a written consent form approved by the IRB (See Section 5.6).

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 WVU.

5.1 Definitions

Legally Authorized Representative. A legally authorized representative is an individual or body authorized under applicable law to provide permission on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. For the purposes of this policy, a legally authorized representative includes not only a person appointed as a health care agent under a Durable Power of Attorney for Health Care (DPAHC), a court appointed guardian of the person, but also next-of-kin in the following order of priority unless otherwise specified by applicable state law: spouse, adult child (18 years of age or older), parent, adult sibling (18 years of age or older), grandparent, or adult grandchild (18 years of age or older).

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

5.2 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 WVU HRPP. Investigators are required to obtain legally effective informed consent from a subject or the subject's Legally Authorized Representative.

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 and signing the informed consent document. The informed consent process is the critical communication link between the prospective Human Subject and an Investigator, beginning with the initial approach of an Investigator and continuing through the completion of the Research study. Investigators must have received the appropriate training and be knowledgeable about the study Protocol in order that they may answer questions to help provide understanding to the study participant or potential study participant. The exchange of information between the Investigator and study participant can occur via one or more of the following modes of communication, among others: face to face contact, mail, telephone, or fax; however, obtaining informed consent must be obtained face to face between the Investigator and the potential study participant unless the IRB allows a modified process.

Investigators must obtain consent prior to entering a subject into a study and/or conducting any procedures required by the protocol, unless consent is waived by the IRB.

If someone other than the investigator conducts the interview and obtains consent from a patient or subject, 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 be able to answer questions about the study.

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.

5.3 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, consent must be obtained from a legal guardian or a legally authorized representative.
2. 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.

3. The informed consent process shall be sought under circumstances that minimize the possibility of coercion or undue influence.
4. 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.
5. 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 conferences include a reliable translator when the prospective subject does not understand the language of the person who is obtaining consent.
6. 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, WVU employees or agents are released from liability for negligence, or appear to be so released.
7. The PI is responsible for insuring that each prospective subject is adequately informed about all aspects of the research and understands the information provided.

5.4 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; a description of any reasonably foreseeable **risks** or discomforts to the subject;
2. A description of any **benefits** to the subject or to others which may reasonably be expected from the research;
3. A disclosure of appropriate **alternative procedures** or courses of treatment, if any, that might be advantageous to the subject;
4. A statement describing the extent, if any, to which **confidentiality** of records identifying the subject must be maintained;
5. For research involving more than minimal risk, an explanation as to the availability of medical treatment in the case of **research-related injury**, including who will pay for the treatment and whether other financial compensation is available;

- a. According to Title 38 CFR 17.85 “Treatment of Research-Related Injuries to Human Subjects,” VA must provide necessary medical treatment to a research subject injured by participation in a research project approved by a VA R&D Committee and conducted under the supervision of one or more VA employees. Except in limited circumstances, the necessary care must be provided in VA medical facilities. Exceptions include: situations where VA facilities are not capable of furnishing economical care; situations where VA facilities are not capable of furnishing the care or services required; and situations involving a non-veteran research subject. Under these circumstances, the medical center Director may contract for such care. This requirement does not apply to treatment for injuries that result from noncompliance by a research subject with study procedures. The informed consent form needs to include language explaining VA’s authority to provide medical treatment to research subjects injured by participation in a VA research project.
 - b. For VA research, all regulations pertaining to the participation of veterans as participants including requirements for indemnification in case of research-related injury pertained to non-veteran participants enrolled in VA-approved research.
6. An **explanation of whom to contact** on the research team for answers to pertinent questions about the research or to voice concerns or complaints about the research, and whom to contact in the event of a research-related injury to the subject;
 7. **Contact information for the IRB** to obtain answers to questions about the research; to voice concerns or complaints about the research; to obtain answers to questions about their rights as a research participant; in the event the research staff could not be reached; and in the event the subject wishes to talk to someone other than the research staff.
 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**, the possibility that the Food and Drug Administration may inspect the records needs to be included in the statement regarding subject confidentiality.
 10. For **clinical trials**, by federal regulation the following required language must be incorporated verbatim and **cannot be altered in any way**:

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

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, which are currently unforeseeable. (For example: Include when the research involves investigational test articles or other procedures in which the risk to subjects is not well known.)
2. A statement that if the subject is or becomes pregnant, the particular treatment or procedure may involve risks to the embryo or fetus, which are currently unforeseeable. (For example: Include when the research involves pregnant women or women of childbearing potential and the risk to fetuses of the drugs, devices, or other procedures involved in the research is not well known.)
3. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent. (For example: Include when there are anticipated circumstances under which the investigator may terminate participation of a subject.)
4. Any additional costs to the subject that may result from participation in the research. (For example: Include when it is anticipated that subjects may have additional costs.)
5. The consequences of a subject's decision to withdraw from the research. (For example: Include when withdrawal from the research is associated with adverse consequences.)
6. Procedures for orderly termination of participation by the subject. (For example: Include when the protocol describes such procedures.)
7. 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. (For example: Include when the research is long term and interim information is likely to be developed during the conduct of the research.)
8. The approximate number of subjects involved in the study. (For example: Include when the research involves more than minimal risk.)

5.5 Documentation of Informed Consent

Except as provided in Section 5.9 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.
2. A copy of the signed and dated consent form must be given to the person signing the form.
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.

When this method is used:

- i. the oral presentation and the short form written document (see sample on ORIC website) 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; 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 English, (i) the oral presentation and the short form written document (see sample attached) 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 a translator, the translator may serve as the witness.

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

For research conducted at the **LAJVAMC**, the **VA Form 10-1086**, Research Consent Form, must be used. IRB approval of the wording of the consent must be documented through the use of a signature and date on each page. This indicates the date of the most recent IRB approval of the document and the expiration date. The consent form must also be approved by the R&D committee. If the consent form is amended during the protocol approval period, the form must bear the approval date of the amendment rather than the date of the approved protocol. The amended consent form must also be approved by the R&D committee.

5.6 Special Consent Circumstances

5.6.1 Non-English Speaking Subjects

Expected enrollment of non-English speaking subjects: In some protocols, the PI expects non-English speaking subjects to enroll because, for example, the protocol is studying a disease or condition that is likely to attract them or the PI is actively recruiting them. When the study subject population includes non-English speaking people or the PI and/or the IRB anticipates that consent discussions will be conducted in a language other than English, the IRB shall require a translated consent document to be prepared. In order to assure itself that the translation is accurate, the IRB may choose to require a certified translation, to have an independent back translation or to have a review of the consent document by an IRB member or other person who is fluent in that language. When non-English speaking subjects enroll, they and the witness sign the translated document. The subjects are given a copy of the signed translated consent document.

1. **Unexpected enrollment of a non-English speaking subject:** If a non-English speaking subject is unexpectedly eligible for protocol enrollment, there may not be an extant IRB-approved written translation of the consent document. 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 at the signing of the consent document or in subsequent discussions, his/her consent may not be informed, and therefore, not effective.

If a PI decides to enroll a subject into a protocol for which there is not an extant IRB-approved informed consent document in the prospective subject's language, the PI must receive IRB approval to follow the procedures for a "short form" written consent in as described in Section 5.5 (3b).

2. **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 deliver information in the IRB-approved script and to facilitate the consent conversation. 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 short form and the IRB-approved consent script well before (24 to 48 hours if possible) the consent conversation with the subject. If the interpreter also serves as the witness, she/he may sign the 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 progress notes of the subject's medical record, including the name of the interpreter.

5.6.2 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 verbal consent will be obtained, witnessed and documented as described below.

5.6.3 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 verbally 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 5.9.

For more 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 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 verbal 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 verbal consent. The consent process will also be documented in the medical record or in accord with WVU procedures. 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.

5.7 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 (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)
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 is not being conducted appropriately.

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 Chair and the Director will develop a monitoring plan and submit it to the IRB for approval. The consent monitoring may be conducted by IRB staff, IRB members or another party, either affiliated or not with the institution. The PI will be notified of the IRB's determination and the reasons for the determination. Arrangements will be made with the PI for the monitoring of the consent process for a specified number of subjects. When observing the consent process, the monitor will determine:

- Whether the informed consent process was appropriately completed and documented,
- Whether the participant had sufficient time to consider study participation,
- Whether the consent process involved coercion or undue influence,
- 6. 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.

5.8 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. In these circumstances, questions sometimes arise about: (1) whether the investigator may use, study, or analyze already collected data about the subject who withdraws from the research or whose participation is terminated by the investigator; and (2) whether the investigator can continue to obtain data about the subject and if so, under what circumstances. The following addresses these and related questions. 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 and informed consent documents.

Regulatory requirements regarding the retention and use of data after subject withdrawal or termination differ between research subjects to FDA regulations and that not subject to FDA regulations. Under applicable FDA law and regulations, data collected on human subjects enrolled in an FDA-regulated clinical trial up to the time of subject withdrawal must remain in the trial database in order for the study to be scientifically valid. For research not subject to FDA regulations, investigators, in consultation with the funding agency, can choose to 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 seeking informed consent from subjects, the following information regarding data retention and use must be included:

1. 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.
2. 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.

Sometimes, a subject wants to withdraw from the primary interventional component of a study, but is willing to allow the investigator to continue other research activities described in the IRB-approved protocol and informed consent document that involve participation of the subject, such as: (1) obtaining data about the subject through interaction with the subject (e.g., through follow-up interviews, physical exams, blood tests, or radiographic imaging); or (2) obtaining identifiable private information from the subject's medical, educational, or social services agency records or from the subject's healthcare providers, teachers, or social worker. 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. Investigator 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 continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through noninvasive chart review, 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 of associated clinical outcome information 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 informed consent form). IRB approval of informed consent documents would be required.

If a subject a) withdraws from the interventional portion of a study, (b) does not consent to continued follow-up of associated clinical outcome information, and (c) does not request removal of their data, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. 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

5.9 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 set forth above; or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

- (a) The research involves no more than minimal tangible or intangible 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 must 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.
- (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 emergency situations (See Section 7.4.3).

5.10 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; or

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 researchers.)

Note 2: In order to waive written documentation of consent where the only record linking the participant and the research would be the consent document, the IRB has to determine that the research was not FDA-regulated.
2. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Procedures such as non-sensitive surveys, questionnaires

and interviews generally do not require written consent when conducted by non-researchers.

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.

5.11 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 HHS 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 (participants) who are in need of emergency medical intervention cannot provide legally effective informed consent and their legally authorized representatives (LARs) are unable to give informed consent as well.

The Secretary of Health and Human Services (HHS) has implemented an Emergency Research Consent Waiver under *45 CFR 46.101(i)* with provisions identical to those of the FDA with the exception of the IND/IDE requirement and the definition of family member includes spouses of brother/sisters. The waiver is not applicable to research involving prisoners, see *45 CFR 46.101(i) & 46.306(b)*.

NOTE – Waiver of informed consent for planned emergency research is not allowed for VA research.

5.11.1 Definition

Planned Emergency Research is research that involves participants (subjects) who, are in a life-threatening situation that makes intervention necessary, but because of their condition (e.g., unconsciousness) are unable to give informed consent, and to be effective, the research intervention needs to be administered before obtaining informed consent from the subject's legally authorized representative is reasonably possible.

5.11.2 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 clinical investigation.

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

- (i) Subjects are facing a life-threatening situation that necessitates intervention;
- (ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
- (iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

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

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

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sections 46.116 and 46.117 of 45 CFR 46 and Sections 20, 25 and 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 clinical investigation consistent with paragraph (7)(v) of this section.

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

- (i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
- (ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the

clinical investigation, of plans for the investigation and its risks and expected benefits;

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

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

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

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

5.11.2.1 FDA-regulated Research

1) 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 such studies as protocols that 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 of CFR Title 21.

2) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph 5.8 (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and

to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRBs that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

3) The IRB determinations and documentation required in Section 5.8 and paragraph 2 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) of CFR Title 21.

5.11.2.2 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 in Section 5.8 have been met relative to the research

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

5.11.3 Community Consultation

Community Consultation assures that the concerns of the community in which emergency research will take place are addressed during the research review process. The plan for community consultation must be approved by the IRB Chair or designee. The PI is responsible for obtaining community consultation, incorporating community concerns into the written protocol and providing information on community concerns to the IRB for their review. Community consultation may include any of the following activities:

- Surveys or questionnaires,
- focus groups or
- community meetings.

If community meetings are held, the meetings must include the Principal Investigator, a representative from the institution, and where required by the IRB, a member of the IRB.

Populations surveyed for the Community Consultation should include those in the community in from which the subjects will be drawn, especially those affected by the disease or condition under study.

Information provided for community consultant consideration includes the investigational plan, its risks and its expected benefits to the individual and to the community.

5.12 Protocol Amendments without Consent Form Changes

During the course of most research studies, the protocol is usually amended for a variety of reasons from additions/deletions of personnel to procedure changes or other administrative changes. When each protocol amendment is approved, "last amended" date listed on the consent form is automatically updated to be congruent with the day that the amendment was approved within the electronic system regardless of whether or not the amendment requested any consent form changes.

Each newly enrolled subject should sign the most recent version of the consent as indicated by the "last amended date" at the time of enrollment.

5.13 Protocol Amendments with Consent Form Changes

When a protocol amendment includes consent form changes, the IRB considers whether or not such changes require re-consenting of subjects. In many cases, such changes are administrative in nature (i.e., fixing misspelled words, addition of personnel, etc.) that do not materially change study procedures, alter the level of risk, or include significant new findings. In such cases it is common for the IRB to determine that subjects already enrolled do not have to sign an updated consent form. When such a determination is made (i.e. re-consenting is not necessary), subjects that have already been enrolled may have signed a consent form with a "last amended" date that is older than the most recently approved consent form's "last amended" date within the system.

 <p>West Virginia University Human Research Protections Program (HRPP) Office of Research Integrity & Compliance STANDARD OPERATING PROCEDURES</p>	<p>Section #: 6 Title: <i>Vulnerable Subjects in Research</i> Date: December 10, 2010 Page: Page 109 of 194</p>
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6 Vulnerable Subjects in Research

When some or all of the participants in a research project conducted under the auspices of WVU 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 WVU.

6.1 Definitions

Minors are persons under the age of eighteen years. (W.Va. Code Sec. 2-2-10) The general rule in West Virginia is that a person who is eighteen years of age or older may execute any legal or other written instrument or deal in his/her own affairs in any manner whatsoever. (W.Va. Code Sec. 2-3-1) Therefore, the WVU IRB hereby defines minors as persons under eighteen years of age.

Certain West Virginia statutes provide minors with "majority" status in some circumstances. For example: A minor over sixteen may petition a court to be declared emancipated. The court may then for cause shown declare the minor to be emancipated. A minor over the age of sixteen who marries is considered emancipated by operation of law. An emancipated minor has all of the privileges, rights and duties of an adult, including the right of contract. (W.Va. Code Sec. 49-7-27)

A written consent to medical treatment pertains to a person's "own affairs" and is a written contract. This also applies to participation in research. Absent specific West Virginia case law or statute to the contrary, persons who are eighteen years of age or older and emancipated minors may execute such contracts under the above laws.

If any specific issues arise under West Virginia law, the WVU IRB will review them on a case by case basis with the WVU General Counsel.

NOTE: For research conducted in jurisdictions other than West Virginia, the research must comply with the laws regarding the legal age of consent or to enter contracts in the relevant jurisdictions. Counsel will provide assistance with regard to the laws in other jurisdictions.

Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child, or other protected person, to general medical care. In WV a “Guardian” of a minor means a person appointed by the court who is responsible for the personal affairs of a protected person to make health care decisions for that minor or protected person to ensure that a patient's right to self-determination in health care decisions be communicated and protected by a person who will act in accordance with the protected person or minor's expressed values and wishes, or, if those values and wishes are unknown, in the protected person's (or minor's) best interests. (W.Va. Code 49-1-4; W.Va. Code 16-30-2&3; W.Va. Code 44A-1-1; W.Va. Code 2-3-1)

NOTE: For research conducted in jurisdictions other than WV, the research must comply with the laws regarding guardianship in all relevant jurisdictions. The General Counsel of the Organization's Office will provide assistance with regard to the laws in other jurisdictions.

Fetus means the product of conception from implantation until delivery.

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

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

Neonate means a newborn.

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

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

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 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.

Surrogate Consent is consent obtained from a legally authorized representative on behalf of a participant determined to lack decision-making capacity.

6.2 Involvement of Vulnerable Populations

When some or all of the participants in a protocol are likely to be vulnerable to coercion or undue influence, the IRB should include additional safeguards to protect the rights

and welfare of these participants. Some of the vulnerable populations that might be involved in research include children, pregnant women, fetuses, neonates, prisoners, or adults who lack the ability to consent, students, employees, or homeless persons.

If the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process will include one or more individuals who are knowledgeable about or experienced in working with these participants. For example, the IRB will include one or more individuals who are knowledgeable about or experienced in working with children, prisoners, or adults with limited decision-making capacity, when reviewing research that involves individuals from these populations.

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-funded 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.

Under WVU's FWA the subparts only apply to DHHS-funded research and research funded by another federal agency that requires compliance with the subparts (FDA regulations include Subpart D, which applies to all FDA-regulated research). The following policies and procedures, which are based on the subparts, apply to all research regardless of funding. The individual sections describe how the subparts apply to DHHS-funded research.

6.3 Responsibilities

1. The PI is responsible for identifying the potential for enrolling vulnerable subjects in the research proposal. The PI is responsible for identifying patients who are at risk for impaired decisional capacity as a consequence of psychiatric illness, 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 ad hoc consultants, individual(s) interested in or who have experience with the vulnerable populations involved in a research proposal.
3. The IRB reviews the PI's justifications for including vulnerable populations in the research to assess appropriateness of the research proposal.
4. The IRB must ensure that additional safeguards have been included in each study to protect the rights and welfare of vulnerable subjects as needed 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 as members of specific vulnerable populations.
6. For studies that do not have or are not required to have a Data and Safety Monitoring Board (DSMB) or a Data Monitoring Committee and have entered vulnerable subjects, the IRB needs to carefully review the safety monitoring plan.
7. The IRB should be knowledgeable about and experienced in working with populations who are vulnerable to coercion and undue influence. If the IRB requires additional qualification or expertise to review a protocol, it should obtain consultation.

6.4 Procedures

Initial Review of Research Proposal:

1. The PI should identify the potential to enroll vulnerable subjects in the proposed research at initial review and provide the justification for their inclusion in the study.
2. The IRB evaluates the proposed plan for consent of the specific vulnerable populations involved. If the research involves adults unable to consent, the IRB evaluates the proposed plan for permission of legally authorized representatives.
3. The IRB evaluates and approves the proposed plan for the assent of participants.
4. The IRB evaluates the research to determine the need for additional protections and consider the use of a data and safety monitoring board or data monitoring committee as appropriate.
5. The PI should provide appropriate safeguards to protect the subject's rights and welfare, which may include the addition of an independent monitor. The independent monitor is a qualified individual not involved in the research study who will determine the subject's capacity to provide voluntary informed consent.
6. Examples of studies that warrant independent monitoring include those involving schizophrenic patients who will be exposed to placebo, and/or drug washout, and/or treatment with agents that are not approved by the Food and Drug Administration (FDA). Populations requiring independent monitoring would include individuals with schizophrenia, other psychotic disorders or conditions characterized by lack of reality testing (i.e., psychosis). Populations not usually requiring independent monitoring would include those with substance use disorders.
7. The IRB assess the adequacy of additional protections for vulnerable populations provided by the PI.

Continuing Review and Monitoring. At Continuing review the PI should identify the number of vulnerable subjects enrolled and any that needed an independent monitor in the progress report.

6.5 Research Involving Pregnant Women, Human Fetuses and Neonates

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

6.5.1 Research Involving Pregnant Women or Fetuses

6.5.1.1 Research Not Funded by DHHS

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

Pregnant women or fetuses may be involved in research not funded by DHHS involving more than minimal risk to 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 who are pregnant, assent and parental consent are obtained in accord with the provisions of permission and assent;
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.

6.5.1.2 Research Funded by DHHS

For DHHS-funded research, 45 CFR Subpart B applies to all research involving pregnant women. Under 45 CFR Subpart B, pregnant women or fetuses may be involved in research funded by DHHS 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 risk 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 pregnant 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 who are pregnant, assent and parental consent are obtained in accord with the provisions of permission and assent in Section 6.7.2;
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.

6.5.2 Research involving neonates

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

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
3. Individuals engaged in the research will have no part in determining the viability of a neonate.
4. The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below in this section) have been met as applicable.

Neonates of Uncertain Viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart 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 covered by this subpart 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.
6. 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.

Viable Neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of IRB Review Process and Research Involving Children.

6.5.3 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 this manual are applicable.

6.5.4 Research Not Otherwise Approvable

6.5.4.1 Research Not Funded 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 of Section 6.2.3, 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.

6.5.4.2 Research Funded by DHHS

DHHS-funded 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.

6.5.5 VHA Regulations: Pregnant Women and Fetuses As Vulnerable Populations

a. Research in which the subject is a fetus, in-utero or ex-utero (including human fetal tissue) must not be conducted by VA investigators while on official duty, or at VA facilities, or at approved off-site facilities.

b. Research related to in vitro fertilization must not be conducted by VA investigators while on official duty, or at VA facilities, or at approved off-site facilities.

6.6 Research Involving Prisoners

Prisoners are another of the three classes that are deemed so vulnerable to exploitation in research that there are special rules protecting them. In the past, prisoners were viewed as a convenient research population. They are housed in a single location, constitute a large and relatively stable population, and live a routine life. Unfortunately, all the things that make a prison and prisoners a convenient research population also make prisoners ripe for exploitation.

The concern Subpart C and this policy based on Subpart C attempt to address is whether prisoners have any real choice in participation in research, or whether incarceration prohibits free choice.

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 research.

6.6.1 Applicability

This policy applies to all biomedical and behavioral research conducted under the auspices of ORIC involving prisoners as subjects. Even though a WVU IRB may approve a research protocol involving prisoners as subjects according to this policy, investigators are still subject to the Administrative Regulations of the West Virginia Division of Corrections and any other applicable State or local law. [45 CFR 46.301]

6.6.2 Minimal Risk

The definition of minimal risk in the Subpart C is different than in the rest of the federal regulations. According to 45 CFR 46.303, minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

6.6.3 Composition of the IRB

In addition to satisfying the general requirements detailed in the IRB section of this manual, 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. The prisoner representative may be listed as an alternative member who becomes a voting member when needed.

6.6.4 Review of Research Involving Prisoners

1. The prisoner representative must review research involving prisoners, focusing on the requirements in Subpart C.
2. The prisoner representative must receive all review materials pertaining to the research (same as primary reviewer)
3. 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.
4. The prisoner representative must present his/her review either orally or in writing at the convened meeting of the IRB when the research involving prisoners is reviewed.
5. 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).
6. 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).
7. 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. The prisoner representative must concur with the determination that the research involves no greater than minimal risk. The prisoner representative must review the research as a reviewer, designated by the chair, or consultant. This may be as the sole reviewer or in addition to another reviewer, as appropriate. Review of modifications and continuing review must use the same procedures for initial review using this expedited procedure including the responsibility of the prisoner representative.
- b. Research that does not involve interaction with prisoners (e.g. existing data, records review) 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 or consultant if designated by the IRB chair. Review of modifications and continuing review must use the same procedures as initial review.

6.6.5 Incarceration of Enrolled Subjects

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

1. Confirm that the participant meets the definition of a prisoner.
2. Terminate enrollment or review the research study under Subpart C if it is feasible for the participant to remain in the study.
3. Before terminating the enrollment of the incarcerated participant the IRB should consider the risks associated with terminating participation in the study. If the participant cannot be terminated for health or safety reasons, 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, 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, keep the participant enrolled.
 - b. If the temporary incarceration has an effect on the study, handle according to the above guidance.

6.6.6 Additional Duties of the IRB

In addition to all other responsibilities prescribed for IRB in the WVU Institutional Review Board and IRB Review Process 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]:
 - 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 social and psychological problems such as alcoholism, drug addiction, and sexual assaults);
 - research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject.
- 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 principal 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 Board 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.

6.6.7 Certification to HHS

Under 45 CFR 46.305(c), the institution responsible for conducting research involving prisoners that is supported by HHS shall certify to the Secretary (through OHRP) that the IRB has made the seven findings required under 45 CFR 46.305(a). For all HHS conducted or supported research WVU 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 protocol in question and any relevant HHS grant application or protocol. HHS conducted or supported research involving prisoners as subjects may not proceed until OHRP issues its approval in writing to WVU 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, any relevant HHS 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.

The above requirement does not apply to research that is not HHS conducted or supported.

6.6.8 Waiver for Epidemiology Research

The Secretary of DHHS has waived the applicability of 45 CFR 46.305(a)(1) and 46.306(a)(2) for certain research conducted or supported by DHHS that involves epidemiologic studies that meet the following criteria:

1. In which the sole purposes are
 - a. To describe the prevalence or incidence of a disease by identifying all cases, or
 - b. To study potential risk factor associations for a disease, and
2. Where the IRB has approved the research and fulfilled its duties under 45 CFR 46.305(a)(2)–(7) and determined and documented that
 - a. The research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
 - b. Prisoners are not a particular focus of the research.
3. The specific type of epidemiological research subject to the waiver involves no more than minimal risk and no more than inconvenience to the human subject participants. The waiver would allow the conduct of minimal risk research that does not now fall within the categories set out in 45 CFR 46.306(a)(2).

4. The range of studies to which the waiver would apply includes epidemiological research related to chronic diseases, injuries, and environmental health. This type of research uses epidemiologic methods (such as interviews and collection of biologic specimens) that generally entail no more than minimal risk to the subjects.
5. In order for a study to be approved under this waiver, the IRB would need to ensure that, among other things, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data.

6.6.9 VHA Regulations: PRISONERS AS A VULNERABLE POPULATION IN RESEARCH.

Prisoners are considered a vulnerable population because both their incarceration and the constraints imposed on them during their incarceration may render them unable to make a truly informed and voluntary decision regarding whether or not to participate as subjects in research. Therefore, research involving prisoners must not be conducted by VA investigators while on official duty, or at VA-approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer. If the waiver is granted, the research must be in accordance with applicable Federal regulations pertaining to prisoners as research subjects (see 45 CFR Part 46, Subpart C 46.301 – 46.306, Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects). NOTE: Requirements for requesting a waiver may be obtained by contacting the Office of Research and Development at VA Central Office or by accessing the VA research web site at <http://www.va.gov/resdev>.

6.7 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.

6.7.1 Allowable Categories

Research on children must be reviewed and categorized by the IRB into one of the following groups:

1. Research not involving physical or emotional risk greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (i.e., **minimal risk**).
 - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 6.7.2
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject.
 - The risk is justified by the anticipated benefit to the subjects;

- Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 5.
3. Research involving greater than minimal risk and no reasonable prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition.
- 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;
 - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 5.
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children.
- Federally-funded research in this category must be approved by the Secretary of Health and Human Services;
 - FDA-regulated research in this category must be approved by the Commissioner of Food and Drugs.
 - For non-federally-funded, non-FDA research, 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
 - Informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of this manual.
 - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 5.

6.7.2 Parental Permission and Assent

6.7.2.1 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 5.4.

The IRB may find that the permission of one parent is sufficient for research to be conducted under Categories 1 & 2 above. The IRB's determination of whether consent must be obtained from one or both parents will be documented in the consent checklists when a protocol receives expedited review, and in meeting minutes when reviewed by the convened committee.

Consent from both parents is required for research to be conducted under Categories 3 & 4 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 consent from a parent or legal guardian if:

- The research meets the provisions for waiver in Section 5.9 or
- If the IRB determines that the research protocol is designed for conditions 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 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, the risk and anticipated benefit to the research subjects, and their 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 5.5 and 5.9.

6.7.2.2 Assent from Children

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. When judging whether children are capable of assent, the IRB is charged with taking into account the ages, maturity, and psychological state of the children involved. The IRB has the discretion to judge children's capacity to assent for all of the children to be involved in a proposed research activity, or on an individual basis.

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.

The IRB presumes that children ages 7 and older should be given an opportunity to provide assent. Oral assent through the use of a script may be obtained from children 7 - 11 years of age. Written assent using a written document for the children to sign may be sought for older children.

At times there may be inconsistency between parent permission and child assent. Usually a "no" from the child overrides a "yes" from a parent, but a child typically cannot decide to be in research over the objections of a parent. Obviously, there are individual exceptions to these guidelines (such as when the use of an experimental treatment for a life threatening disease is being considered). The general idea, however, is that children should not be forced to be research subjects, even when their parents consent to it.

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

Even when the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances detailed in the Waiver of Informed Consent section of this manual.

The Assent Form

When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

Researchers should try to draft a 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.

For younger children, the document should be limited to one page if possible. Illustrations might be helpful, and larger type makes a form easier for young children to read. Studies involving older children or adolescents should include more information and may use more complex language.

6.7.2.3 Children Who are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition, **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.

6.7.3 VHA Regulations: CHILDREN AS A VULNERABLE POPULATION IN RESEARCH.

VA is authorized to care for veterans and to conduct research that supports the mission of VHA and that enhances the quality of health care delivery to veterans. Therefore, research involving children must not be conducted by VA investigators while on official duty or at VA or approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer. If the waiver is granted, the research must be in accordance with applicable Federal regulations pertaining to children as research subjects (see 45 CFR Part 46, Subpart D 46.401 – 46.409, Additional Protections for Children Involved as Subjects in Research). NOTE: For requirements for requesting a waiver contact 202-254-0183.

6.8 Persons with Impaired Decision Making Capacity

The requirements in this section apply to all research involving persons with mental disabilities or persons with impaired decision-making capacity regardless of funding source.

Research involving persons with impaired decision-making capability may only be approved when the following conditions apply:

1. Only incompetent persons or persons with impaired decision making capacity are suitable as research subjects. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects. Incompetent persons or persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.
2. The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.
3. Procedures have been devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity. Health care agents (appointed under Durable Power of Attorney for Health Care (DPAHC)) and next-of-kin, or guardians, must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.

6.8.1 IRB composition

The IRB membership must include at least one member who is an expert in the area of the research. Consideration may be given to adding another member who is a member of the population, a family member of such a person or a representative of an advocacy group for that population. The IRB may utilize ad hoc members as necessary to ensure appropriate scientific expertise.

6.8.2 Determination of Decision-Making Capacity

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.

For research protocols that involve subjects with mental disorders that may affect decision-making capacity, the IRB may determine that capacity assessments are necessary, unless the investigator can justify why such assessments would be unnecessary for a particular group.

For research that poses greater than minimal risk, the IRB may require investigators to use independent and qualified professionals to assess whether potential subjects have the capacity to give voluntary, informed consent. Even in research involving only minimal risk, the IRB may require that the study include a capacity assessment if there are reasons to believe that potential subjects' capacity may be impaired. It is not necessary to require a formal capacity assessment by an independent professional for all potential research subjects with mental disorders.

For research protocols involving subjects who have fluctuating or limited decision making capacity the IRB may ensure that investigators establish and maintain ongoing communication with involved caregivers. Periodic re-consent should be considered in some cases. Third party consent monitors may be used during the recruitment and consenting process, or waiting periods may be required to allow more time for the subject to consider the information that has been presented.

It is often possible for investigators and others to enable persons with some decisional impairments to make voluntary and informed decisions to consent 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, interpreter for hearing-impaired subjects, 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 give consent, a re-consenting process with surrogate consent may be necessary.

Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

In the event research participants become incompetent or impaired in decision making capacity after enrollment, the PI is responsible for notifying the IRB and the ORIC. The PI is responsible for developing a monitoring plan which follows the guidelines outlined above for incompetent and impaired decision making research participants.

6.8.2.1 Procedures for Determining Capacity to Consent

Decisional capacity in the research context has been interpreted by the American Psychiatric Association as requiring:

1. Ability to evidence a choice,
2. Ability to understand relevant information,
3. Ability to appreciate the situation and its likely consequences, and
4. Ability to manipulate information rationally.

A range of professionals and methods may be utilized to assess capacity. In general the consent assessor should be a researcher or consultant familiar with dementias and qualified to assess and monitor capacity and consent in such subjects on an ongoing basis. The IRB will consider the qualifications of the proposed individual(s) and whether he or she is sufficiently independent of the research team and/or institution.

The majority of studies conducted at the WVU only allow enrolling subjects who have the capacity to consent. For studies that have been approved for enrolling vulnerable populations who may lack capacity to consent, there must be someone who is able to assess capacity of each potential subject to consent. The PI may determine after appropriate medical evaluation that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time. Additionally, if the reason for lack of capacity is because of mental illness then a psychiatrist or licensed psychologist must confirm this judgment and document in the individual's medical record in a signed and dated progress note.

A person who has been determined to lack capacity to consent to participate in a research study must be notified of that determination before permission may be sought from his or her legally authorized representative to enroll that person in the study. If permission is given to enroll such a person in the study, the potential subject must then be notified. Should the person object to participating, this objection should be heeded.

6.8.3 Informed Consent and Assent

Whenever the participants have the capacity to give consent (as determined by qualified professionals), informed consent should be obtained and documented in accordance with Section 5 above. When participants lack the capacity to give consent, investigators may obtain consent from the legally authorized representative of a subject (surrogate consent) as described below.

A person who is incompetent or has been determined to lack capacity to consent to participate in a research study should be informed about the trial to the extent compatible with the subject's understanding and, if possible, the subject should give their assent to participate, sign and date the written informed consent or a separate assent form. If the person objects to participating, this objection should be heeded.

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 give consent, a re-consenting process with surrogate consent may be necessary. Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their

representatives. Under no circumstances may subjects be forced or coerced to participate.

6.8.3.1 Surrogate Consent

Surrogate consent may be obtained from a legally authorized representative as described in Section 5.1.

At the LAJVAMC, surrogate consent may be obtained from next-of-kin in the following order of priority, unless otherwise specified by applicable state law: spouse, adult child (18 years or older), parent, adult sibling (18 years of age or older), grandparent, or adult grandchild (18 years of age or older).

- Consent by a legally authorized representative is limited to situations where the prospective participant is incompetent or has impaired decision-making capacity, as determined and documented in the person's medical record in a signed and dated progress note.
- A participant is determined to be incompetent or has an impaired decision making capacity by a legal determination or a determination by the practitioner, in consultation with the Chief of Service or Chief of Staff, after appropriate medical evaluation that the prospective participant lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.
- If the determination that the prospective participant lacks decision-making capacity is based on a diagnosis of mental illness, the Researcher obtains consultation with a psychiatrist or licensed psychologist.
- The practitioner should explain the proposed research to the prospective participant when feasible.
- Participants are prohibited from being forced or coerced to participate in a research study.



**Human Research Protections Program
(HRPP)**

Office of Research Integrity & Compliance

STANDARD OPERATING PROCEDURES

Section #: 7

Title: *FDA-Regulated Research*

Date: December 10, 2010

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7 FDA-Regulated Research

FDA regulations apply to any research that involves a *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, as well as, where appropriate, 45 CFR 46. (See ORIC website.)

Use of investigational drugs must be conducted according to FDA 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 WVU.

7.1 Definitions

Investigational Drug. An investigational drug for clinical research use is one for which the PI or a sponsor has filed an IND application (21 CFR Part 312) or an approved drug that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.

Investigational Device. A medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. As further stated, a device is any healthcare product that does not achieve its primary intended purpose by chemical action or by being metabolized.

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.

Emergency Use. Emergency use is defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

Significant Risk (SR). 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). A non-significant risk device is an investigational device other than a significant risk device.

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

7.2 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 Food and Drug Administration 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)]

7.3 Procedures

- A. At initial submission, the PI must indicate whether the research involves a test article and is a clinical investigation involving human subjects on the application form. The PI may use the Human Subjects Research Determination Form to assist in making this determination.
- B. During the pre-review process, the IRB Administrator will confirm whether FDA regulations are applicable using the Human Subjects Research Determination Form. If FDA regulations apply and the research is not exempt, the IRB Administrator will indicate on the agenda that the protocol is an FDA-regulated study.

- C. If required by the sponsor (see Section 1.5), the PI will indicated on the application form that ICH-GCP compliance is required and will affirm compliance. If the study involves investigational drugs and is industry sponsored and the PI does not indicated ICH-GCP compliance, the IRB Administrator will confirm with the Office of Sponsored whether ICH-GCP compliance is required and obtain PI affirmation of compliance.

7.4 Investigational Drugs and Devices in Research

7.4.1 IND/IDE Requirements

The PI must indicate on the IRB application whether the research involves investigational drugs or devices. If so, the PI must indicate if there is an IND/IDE for the research and provide documented assurance from the sponsor that the manufacture and formulation of investigational or unlicensed test articles conform to federal regulations. Documentation of the IND/IDE could be a:

1. Industry sponsored protocol with IND/IDE.
2. Letter from FDA.
3. Letter from industry sponsor.
4. Other document and/or communication verifying the IND/IDE.

For investigational devices, NSR device studies follow abbreviated IDE requirements and do not have to have an IDE application approved by the FDA. If a sponsor has identified a study as NSR, then the investigator must provide an explanation of the determination. If the FDA has determined that the study is NSR, documentation of that determination must be provided.

If the research involves drugs or devices and there is no IND/IDE, the PI must provide a rationale why it is not required.

The IRB will review the application and determine:

1. Whether there is an IND/IDE and if so, whether there is appropriate supporting documentation.
2. If the research involves drugs or devices with no IND/IDE, and whether the research meets the criteria below.

7.4.1.1 IND Exemption

For drugs, an IND is not necessary if the research falls in one of the following 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 in support of a new indication for use or to support any other significant change in the labeling for the drug
 - b. 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 or dosage level, use in a 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 concerning the promotion and sale of drugs [21 CFR 312.7]
 - 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 21 CFR 312.160
 4. A clinical investigation involving the use of a placebo if the investigation does not otherwise require submission of an IND.

7.4.1.2 Exempted IDE Investigations

For 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;
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.

7.4.2 Responsibilities

7.4.2.1 PI

1. The PI is responsible for ensuring that the research is conducted according to all regulatory guidelines and WVU policies and procedures
2. The PI must obtain approval from the IRB before initiating any research activities.
3. The PI proposing the drug/device research will be required to provide a plan – to be evaluated by the IRB - that includes storage, security, and dispensing of the drug/biologics/device.
 - a. The PI is responsible for the investigational drug/device accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability.
 - b. The PI will delegate the responsibility for drugs/biologics accountability to the WVU Hospitals Inc. (WVUH) Department of Pharmaceutical Services (DPS).
 - c. All devices received for a study must be stored in a locked environment under secure control with limited access. The area must be within an area of PI's control. 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.
4. The PI shall report all unanticipated problems involving risk to subjects or others to the IRB according to the procedures outlined in Section 8.
5. For research involving investigational new drugs:
 - a. The PI is required to inform DPS that the IRB has approved the protocol through submission of the IRB approval letters.

- b. The PI must inform the IRB and DPS when a study involving investigational drugs has been terminated by the sponsor.
 - c. The PI will report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug (21 CFR 312 (b)) according to the procedures in the protocol.
 - d. The PI will maintain the following:
 - i. Current curriculum vitae (CV)
 - ii. Protocol
 - iii. Records of receipt and disposition of drugs
 - iv. List of any co-investigators with their curriculum vitae
 - v. Certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation, and
 - vi. Case histories with particular documentation on evidence of drug effects. Emphasis is on toxicity and possible untoward happenings. All unexpected adverse effects are reportable; even if the investigator considers that the event is not related to the drug. All unexpected adverse effects shall be reported immediately to DPS and the IRB in the manner defined by the protocol.
 - vii. IRB letters of approval.
 - viii. Other documents as outlined in the Human Subject Protection Program Policies.
 - e. For VA research, the investigator:
 - i. Informs the pharmacy service of the IRB's and Research and Development Committee's approval through Form 10-1223.
 - ii. Provides the pharmacy with a signed copy of Form 10-1086 to document each participant's consent to participate in the study.
 - iii. Informs the Chief, Pharmacy Service, and the Research and Development Committee when a study involving investigational drugs has been terminated.
1. For research involving investigational devices:
- a) If a device is considered NSR by the PI or sponsor, but after review the IRB determines the device to have significant risk, upon receipt of written notice the PI is responsible for notifying the sponsor of the IRB's determination. The PI must provide the IRB with confirmation of this action.
 - b) If the PI is storing the devices, he/she must maintain a log indicating the identification/serial number of the device, name of subject, date dispensed, by whom it was dispensed, and amount remaining.
 - c) The PI will maintain the following:

- i. Current curriculum vitae (CV),
 - ii. Protocol of the study,
 - iii. Records of animal study reports
 - iv. Records of receipt and disposition of devices
 - v. List of any co-investigators with their curriculum vitae,
 - vi. Certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation,
 - vii. Case histories with particular documentation on evidence of effects. Emphasis is on safety and possible untoward happenings. All adverse device effects are reportable.
 - viii. IRB letters of approval and the Protocol Review Monitoring Committee (PRMC) approval letter if applicable.
 - ix. Device training.
 - x. Other documents as outlined in the Human Subject Protection Program Policies.
 - d) Following completion of the study the termination procedure for investigational drugs must be applied if pharmacy controlled; or if the devices are kept by the investigator, the log must be completed regarding the receipt, use and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.
 - e) If, after use, the PI keeps the devices, he/she must maintain a log regarding the receipt, use and/or re-dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.
 - f) The PI will submit to the sponsor and to the IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
2. When a PI files an IND or IDE, the PI is considered the sponsor and as such is accountable for all of the FDA regulatory responsibilities and reporting obligations of both the PI and the sponsor, as described in the FDA regulations. The Research Plan asks the PI if he/she also acts as the sponsor of the research and, if so, asks him/her to affirm that he/she has reviewed the **Guidance Document on Requirements of the Sponsor and the Investigator as a Sponsor** (see ORIC website) and will comply with the regulatory responsibilities of a sponsor. The ORIC Clinical Research Consultant will conduct education programs for investigators holding an IND or IDE on the sponsor regulations and periodically conduct random audits of PIs holding an IND or IDE as per the Quality Improvement Program.

7.4.2.2 IRB

1. The IRB will review the research in accordance with the following requirements and the same criteria it would use in considering approval of any research involving an FDA-regulated product (21 CFR 56.111).
2. For research involving investigational devices:
 - a. The IRB will review the control plan and determine whether it is adequate. If the Chair determines that the IRB does not have the necessary expertise to evaluate the plan, outside consultation will be used (e.g., Bioengineering).
 - b. Unless the FDA has already made a risk determination for the study, the IRB will review NSR studies and determine if the device represents significant or non-significant risk and report the findings to the PI in writing. The IRB will consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures. Non-significant risk device studies do not require submission of an IDE application but must be conducted in accordance with the abbreviated requirements of IDE regulations.
 - Abbreviated IDE requirements:
 - The device is not a banned device.
 - The sponsor labels the device in accordance with 21 CFR 812.5.
 - The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device was not a significant risk device, and maintains such approval.
 - The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, consent under 21 CFR 50 and documents it, unless documentation was waived.
 - The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations.
 - The sponsor maintains the records required under 21 CFR 812.140(b)(4) and (5) and makes the reports required under 21 CFR 812.150 (b)(1) through (3) and (5) through (10).
 - The sponsor ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 812.150(a)(1), (2), (5) and (7).

- The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

If the study that has been submitted as NSR is considered SR, the IRB may approve the study, but the study cannot begin until an IDE is obtained.

- c. The IRB will not review protocols involving significant risk devices under expedited review.
- d. The IRB will document in the minutes and provide written documentation to the PI of the rationale for determining whether a device is classified as NSR/SR.
- e. If the FDA has already made the SR or NSR determination for the study, the agency's determination is final and the IRB does not need to make a risk determination.

7.4.3 Emergency Use

7.4.3.1 Emergency Exemption from Prospective IRB Approval

HHS regulations do not permit human subjects 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 HHS 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.

FDA defines emergency use as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. 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 utilized.

Informed consent must be obtained in accordance with and to the extent required by 21 CFR 50. Informed consent must be documented in writing in accordance with and to the extent required by 21 CFR 50.27.

The IRB must be notified within 5 working days when an emergency exemption is used. Any subsequent use of the test article at the institution is subject to IRB review. This notification must not be construed as an approval for the emergency use by the IRB. The IRB Chair or designee will review the report to verify that circumstances of the emergency use conformed to FDA regulations and will be placed on the agenda.

7.4.3.2 Emergency Waiver of Informed Consent

An exception under FDA regulations at 21 CFR 50.23 permits the emergency use of an investigational drug, device, or biologic 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;
- d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If time is not sufficient to obtain the independent physician determination before use of the test article, the actions of the investigator must be reviewed and evaluated in writing by an independent physician within 5-6 working days. The IRB must be notified within 5 working days when an emergency waiver is used. This notification must not be construed as an approval for the emergency waiver by the IRB. The IRB Chair or designee will review the report to verify that circumstances of the emergency waiver conformed to FDA regulations and will be placed on the agenda.

7.4.3.3 Expanded Access of Investigational Drugs

FDA regulations allow certain individuals not enrolled in clinical trials to obtain expanded access to investigational drugs, agents, or biologics through the following methods:

1. **Compassionate Use:** The term "compassionate use" is erroneously used to refer to the provision of investigational drugs outside of an ongoing clinical trial to a limited number of patients who are desperately ill and for whom no standard alternative therapies are available. The term "compassionate use" does not, however, appear in FDA or HHS regulations. It is preferable, instead, to use the names of the specific access programs when discussing the use of investigational articles outside of formal clinical trials.
2. **Group C Treatment Investigational New Drug (IND):** A means for the distribution of investigational drugs, agents, or biologics to oncologists for the treatment of cancer under protocols outside controlled clinical trials. Group C drugs, agents, or biologics usually have shown evidence of relative and reproducible efficacy in a specific tumor type. Although the FDA typically grants a waiver for most drugs used in Group C Treatment IND protocols, WVU IRB requires prospective IRB review and approval.
3. **Open – Label Protocol:** A study designed to obtain additional safety data, typically done when the controlled trial has ended and treatment continues. The purpose of such a study is to allow subjects to continue to receive the benefits of the investigational drug, agent, or biologic until marketing approval is obtained. Prospective IRB review and approval is required.

4. **Parallel Track:** A method approved by the FDA that expands the availability of investigational drugs, agents, or biologics as quickly as possible to persons with AIDS and other HIV-related diseases. These drugs, agents or biologics are utilized in separate protocols that “parallel” the controlled clinical trials and are essential to establish the safety and effectiveness of these new drugs, agents, or biologics. Although the Secretary of the Department of Health and Human Services may, on a protocol-by-protocol basis, waive the provisions of 45 CFR Part 46 where adequate protections are provided through other mechanisms, prospective IRB review and approval is required by the WVU IRB.
5. **Treatment IND or Biologics:** A mechanism for providing eligible subjects with investigational drugs (as early in the drug development process as possible) for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. The FDA defines an immediately life-threatening disease as a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. The FDA will permit an investigational drug to be used under a treatment IND after sufficient data have been collected to show that the drug “may be effective” and does not have unreasonable risks. Prospective IRB review and approval is required.
 - a. There are four requirements that must be met before a treatment IND can be issued:
 - i. The drug is intended to treat a serious or immediately life-threatening disease;
 - ii. There is no satisfactory alternative treatment available;
 - iii. The drug is already under investigation or trials have been completed; and
 - iv. The trial sponsor is actively pursuing marketing approval.
 - b. The FDA identifies two special considerations when a patient is to be treated under a Treatment IND:
 - i. **Informed Consent.** Informed consent is especially important in treatment use situations because the subjects are desperately ill and particularly vulnerable. They will be receiving medications which have not been proven either safe or effective in a clinical setting. Both the setting and their desperation may work against their ability to make an informed assessment of the risk involved. Therefore, the IRB should ensure that potential subjects are fully aware of the risks involved in participation.
 - ii. **Charging for Treatment INDs.** The FDA permits charging for the drug, agent, or biologic when used in a Treatment IND. Therefore, the IRB Committee should pay particular attention to Treatment INDs in which the subjects will be charged for the cost of the drugs. If subjects will be charged for use of

the test article, economically disadvantaged persons will likely be excluded from participation. Charging for participation may preclude economically disadvantaged persons as a class from receiving access to test articles. The IRB should balance this interest against the possibility that unless the sponsor can charge for the drug, it will not be available for treatment use until it receives full FDA approval.

6. **Single-Patient Use:** The use of an investigational drug outside of a controlled clinical trial for a patient, usually in a desperate situation, who is unresponsive to other therapies or in a situation where no approved or generally recognized treatment is available. There is usually little evidence that the proposed therapy is useful, but may be plausible on theoretical grounds or anecdotes of success. Access to investigational drugs for use by a single, identified patient may be gained either through the sponsor under a treatment protocol, or through the FDA, by first obtaining the drug from the sponsor and then submitting a treatment IND to the FDA requesting authorization to use the investigational drug for treatment use. Prospective IRB review and approval is required (See 5 above).
7. **Emergency IND:** The emergency use of an unapproved investigational drug, agent, or biologic requires an emergency IND. The FDA has established mechanisms and guidance for obtaining an Emergency IND for the use of investigational drugs, agents, or biologics.

7.4.3.4 Emergency Waiver of IND

FDA regulations at 21 CFR 312.34, 312.35, and 312.36 address the need for an investigational drug to be used in an emergency situation that does not allow time for submission of an IND. The FDA may authorize shipment of the drug for a specific use in such a circumstance in advance of submission of an IND. Prospective IRB review is required unless the conditions for exemption are met (21 CFR 56.104(c) and 56.102(d)). Informed consent is required unless the conditions for exemption are met (21 CFR 50.23). All applicable regulations must be met including those at 21 CFR Parts 50 and 56, and 21 CFR 312.34 and 312.35.

7.4.3.5 Expanded Access of Investigational Devices

1. **Compassionate Use (or Single Patient/Small Group Access).** The compassionate use provision allows access for patients who do not meet the requirements for inclusion in the clinical investigation but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. This provision is typically approved for individual patients but may be approved to treat a small group. It must be a serious disease or condition and no alternative treatment available. Prior FDA approval is needed before compassionate use occurs.
2. **Treatment Use.** An approved IDE specifies the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in the study. During the course of the clinical trial, if the data suggests that the device is

effective, then the trial may be expanded to include additional patients with life-threatening or serious diseases. The criteria include:

- a. Life-threatening or serious disease
 - b. No alternative
 - c. Controlled clinical trial
 - d. Sponsor pursuing marketing approval
3. Continued Access. FDA may allow continued enrollment of subjects after the controlled clinical trial under an IDE has been completed in order to allow access to the investigational medical device while the marketing application is being prepared by the sponsor or reviewed by FDA. There must be a public health need or preliminary evidence that the device will be effective and there are no significant safety concerns.

7.4.3.6 Humanitarian Use Devices (HUD)

In accordance with 21 CFR 814.124, treatment with a HUD is subject to full board initial and continuing review by the IRB. In most cases a cover letter is required to inform the patient. If a physician in an emergency situation determines that IRB approval cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior IRB approval. In this instance, approval must be obtained from the Chief of Staff and the investigator is required to provide written notification of the use to the IRB within five days after use of the device. The IRB requires that written notification include identification (specification without identifiers) of the patient, the date on which the device was used, and the reason for the use. It is the responsibility of the investigator to notify the FDA if the IRB were ever to withdraw approval for use of a HUD. The FDA should be notified within five days of notification of the withdrawal of approval. Investigators are reminded that Humanitarian Device Exemptions are for clinical use only and HUDs can be used only for purposes outlined in the approved IRB application.

7.4.3.7 Waiver of Informed Consent for Planned Emergency Research

The WVU 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 Chapter 5.10 for details on Planned Emergency Research.

 <p>West Virginia University Human Research Protections Program (HRPP) Office of Research Integrity & Compliance STANDARD OPERATING PROCEDURES</p>	<p>Section #: 8 Title: <i>Unanticipated Problems Involving Risks to Subjects or Others</i> Date: December 10, 2010 Page: Page 144 of 194</p>
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8 Unanticipated Problems Involving Risks to Subjects or Others

WVU complies with DHHS and FDA regulations which state that institutions must have written policies on reporting unanticipated problems involving risks to subjects or others to the IRB, institutional officials and relevant federal agencies and departments.

The following procedures describe how unanticipated problems involving risk to subjects or others are handled in research under the auspices of WVU.

8.1 Definitions

Unanticipated problems involving risk to participants or others. Unanticipated problems involving risks to participants or others 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, 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 protocol-related documents, such as the IRB-approved research protocol 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 (AE). An adverse event is defined as any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article.

8.2 Procedures

8.2.1 Reporting

Investigators must promptly report the following problems to the IRB:

1. Adverse events involving direct harm to participants which in the opinion of the principal investigator meet the criteria for an unanticipated problem involving risk to subjects or others.
2. An unanticipated event related to the research that exposes participants to potential risk but that does not involve direct harm to participants.
3. An unanticipated event related to the research that exposes individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to potential risk
4. IND Safety Reports from sponsors that meet the criteria for an unanticipated problem involving risk to subjects.
5. Information that indicates a change to the risks or potential benefits of the research. For example:
 - a. 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.
 - b. A paper is published from another study that shows that the risks or potential benefits of your research may be different than initially presented to the IRB.
6. A breach of confidentiality.
7. Incarceration of a participant in a protocol not approved to enroll prisoners.
8. Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant.
9. Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team.
10. Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm. Protocol violations must be reported ***within thirty (30) days of the PI being made aware of the violation.***
11. Sponsor imposed suspension for risk.
12. Any other event that indicates participant or others might be at risk of serious, unanticipated harms that are reasonably related to the research.

8.2.2 Submission of Reports

Investigators must report possible unanticipated problems to the IRB promptly.

- If the event requires immediate intervention to prevent serious harm to participants or others, the investigator must report the event within five (5) days of receiving notice of the event.
- Investigators must report all other possible unanticipated problems occurring at the local research site and non-local research sites to the IRB as soon as possible but no later than ten (10) business days from the date of the event or from the date the investigator is notified of the event.

Problems occurring within thirty (30) days after participants' active participation or treatment must be reported according to the above schedule.

Investigators or the study team must report possible unanticipated problems to the HRPP in writing using the Unanticipated Problem Reporting Form. The written report should contain the following:

- a. Detailed information about the possible unanticipated problems, including relevant dates.
- b. Any corrective action, planned or already taken, to ensure that the possible unanticipated problems 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 physical, social, or psychological harm and any plan to address these consequences.
- d. Any other relevant information.
- e. Any other information requested by the HRPP.

A report of a possible unanticipated problem involving risks to participants or others will be immediately forwarded by HRPP staff to the IRB Chair if the HRPP staff believes that immediate intervention may be required to protect participants or others from serious harm.

Upon receipt of a report of a possible unanticipated problem from someone other than the investigator or study staff, the IRB director will notify the PI on the study when appropriate.

8.2.3 IRB Procedures for Handling Reports of Possible Unanticipated Problems

8.2.3.1 Review by IRB Staff and Chair

1. Upon receipt of an Unanticipated Problem Involving Risk to Subjects or Others (UPIRTSO) from a Principal Investigator, the IRB support staff checks the form for completeness. If any applicable sections of the form are incomplete or have 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 chairperson and/or other experienced member(s) designated by the IRB chairperson receives and reviews the report of the event(s) considered to be an

unanticipated problem. The IRB chairperson (or designee) will make the final determination as to whether the event is to be regarded as an unanticipated problem.

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.
4. The IRB or the IRB chairperson (or designee) has authority to require submission of more detailed contextual information by the PI, the sponsor, the study coordinating center, or DSMB/DMC about any adverse event occurring in a research protocol as a condition of the continuation of the IRB's approval of the research.
5. If the reviewer considers that either (1) the problem was foreseen OR (2) no participants or others were harmed AND participants or others are not at increased risk of harm, the reviewer indicates on the form that the problem is not an unanticipated problem. The form is filed in the protocol record, the determination is communicated to the investigator and no further action is taken.
6. If the reviewer considers that the problem is an unanticipated problem, but that the risk is no more than minimal, the reviewer will review:
 - a. The currently approved protocol
 - b. The currently approved consent document
 - c. Previous reports of unanticipated problems involving risks to participants or others
 - d. The investigator's brochure, if one exists

After reviewing all of the materials, the reviewer will take appropriate action depending on the nature of the risk involved, including modification of the protocol or the consent form, if applicable. The results of the review will be recorded in the protocol record, communicated to the investigator, and reported to the IRB. All events determined to be unanticipated problems will be reported to the relevant regulatory agencies and institutional officials according to the procedures in Section 11.

7. All reported unanticipated problems where the risk is more than minimal will be reviewed at a convened IRB meeting.

8.2.3.2 IRB Review

The primary reviewer will be given the protocol file, the currently approved consent document, previous reports of unanticipated problems involving risks to participants or others, the investigator's brochure (if one exists), the UPIRSTO report, and recommendations from the IRB Chair or designee, when appropriate. All IRB members will receive the UPIRSTO report.

After review of the protocol and UPIRSTO report, the full IRB will make findings and recommendations based on the following considerations:

- a. Whether the reported event is an unanticipated problem involving risks to participants or others according to the definition in this policy.
 - b. What action in response to the report is appropriate.
 - c. Whether suspension or termination of approval is warranted.
 - d. Whether further reporting to Institutional and/or federal officials is required.
1. If the IRB finds that the event is not an unanticipated problem involving risks to participants or others, 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
 - 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 participant's willingness to continue participation)
 - g. Providing additional information to past participants
 - h. Requiring additional training of the investigator and/or study staff
 - i. Other actions appropriate for the local context
 2. If the IRB finds that the event is an unanticipated problem involving risks to participants or others, according to the definition in the policy, the IRB may recommend any of the following actions:
 - a. Requiring modifications to the protocol
 - 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 participant'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. Requirement that current participants re-consent to participation
 - j. Monitoring of the research
 - k. Monitoring of the consent

- l. Referral to other organizational entities (e.g., legal counsel, institutional official)
 - m. Suspending the research
 - n. Terminating the research
 - o. Other actions appropriate for the local context
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 Vice President for Research, the Director of ORIC, and OHRP, and FDA (if FDA-regulated research) through the Vice President for Research. This should be done in writing.
 4. If, after reviewing a report, the IRB finds that the event is an unanticipated problem involving risks to participants or others 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 (ORO, OHRP, and FDA).

8.3 VA Research

In addition to the general requirements for reporting unanticipated problems, VHA Handbook 1058.01 require the following to be reported to the IRB:

Serious Adverse Event (SAE). An SAE is an adverse event that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect. An adverse event is also considered serious when medical, surgical, behavioral, social, or other intervention is needed to prevent such an outcome.

Serious Unanticipated Problem. A serious unanticipated problem is an event that meets the definition of an unanticipated problem involving risk to subjects or others that may reasonably be regarded as:

- (1) Interruptions of subject enrollments or other research activities due to concerns about the safety, rights, or welfare of human research subjects, research staff, or others.
- (2) Any work-related injury to personnel involved in human research, or any research-related injury to any other person, that requires more than minor medical intervention (i.e., basic first aid), requires extended surveillance of the affected individual(s), or leads to serious complications or death.
- (3) Any VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the facility's research projects.

- (4) Any DMC, DSMB, or DSMC report describing a safety problem.
- (5) Any sponsor analysis describing a safety problem for which action at the facility level may be warranted. **NOTE:** *Sponsor AE reports lacking meaningful analysis do not constitute “problems” under this paragraph.*
- (6) Any unanticipated problem involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others; or
- (7) Any problem reflecting a deficiency that substantively compromising the effectiveness of a facility’s human research protection or human research oversight programs.

Within 5 business days after a report of a serious unanticipated problem involving risks to subjects or others, or of a local unanticipated SAE, the convened IRB or a qualified IRB member-reviewer must determine and document whether or not the reported incident was serious and unanticipated and related to the research. If the convened IRB or the qualified IRB member-reviewer determines that the problem or event is serious and unanticipated and related to the research, the IRB Chair or designee must report the problem or event directly (without intermediaries) to the facility Director within 5 business days after the determination.

All determinations of the qualified IRB member-reviewer (regardless of outcome) must be reported to the IRB at its next convened meeting. If the convened IRB or the qualified IRB member-reviewer determines that the problem or event is serious and unanticipated and related to the research, then:

1. A simultaneous determination is required regarding the need for any action (e.g., suspension of activities; notification of subjects) necessary to prevent an immediate hazard to subjects in accordance with VA regulations at 38 CFR 16.103(b)(4)(iii).
2. If it was determined that the problem or event is serious and unanticipated and related to the research, the convened IRB must determine and document whether or not a protocol or informed consent modification is warranted.
3. If the convened IRB determines that a protocol or informed consent modification is warranted, the IRB must also determine and document:
 - a. Whether or not previously enrolled subjects must be notified of the modification and, if so,
 - b. When such notification must take place and how such notification must be documented.

 <p>West Virginia University Human Research Protections Program (HRPP) Office of Research Integrity & Compliance STANDARD OPERATING PROCEDURES</p>	<p>Section #: 9 Title: <i>Protocol Exceptions or Deviations</i> Date: December 10, 2010 Page: Page 151 of 194</p>
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9 Protocol Exceptions or Deviations

It is the policy of the WVU IRB to be notified of any protocol deviations or exceptions that result in an increase in risk or a decrease in benefit to participants.

The following procedures describe how protocol exceptions and deviations are reported to the IRB.

9.1 Definitions

Exceptions. Protocol exceptions are defined as circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient/subject (example: patient/subject is allergic to one of the medications provided as supportive care). Usually it is a violation that is anticipated and happens with prior agreement from the sponsor.

Deviations. A protocol deviation is defined as a violation that is unanticipated and happens without any prior agreement (protocol visit scheduled outside protocol window, blood work drawn outside protocol window, etc.). The IRB will review these reports for frequency and may audit any protocol reporting frequent deviations.

9.2 Exceptions

It is the responsibility of the Investigator to report to the IRB, exceptions made to the protocol. The IRB will perform an expedited review of the “Deviation/Exception Report” form submitted by the Investigator electronically along with documentation of Sponsor justification and approval.

These exceptions must be approved by the sponsor and IRB before being implemented.

Exceptions may not increase risk or decrease benefit, affect the participant’s rights, safety, welfare, or affects the integrity of the resultant data.

9.3 Deviations

The IRB recognizes that deviations to approved protocols may occur. It is the responsibility of the Principal Investigator to notify the IRB if the deviations may expose

subjects to increased risk or fewer benefits, or if the deviation compromises the integrity of the study.

A protocol deviation or violation occurs when there is a variance in a research study between the protocol and the activities being performed. Protocol deviations may be minor or major as defined below.

Minor protocol deviations:

- The deviation has no substantive effect on the risks or benefits to the individual research subject, AND
- The deviation has no substantive effect on the value of the data collected, AND
- The deviation did not result from willful or knowing misconduct on the part of the investigator(s) or study staff.

Major protocol deviations (protocol violations):

- The deviation has harmed or posed a significant risk of substantive harm to the individual research subject and increased the risk/benefit ratio, OR
- The deviation has compromised the scientific integrity of the data collected for the study, OR
- There is evidence of willful or knowing misconduct on the part of the investigator(s) or study staff, OR
- The investigator(s) or study staff demonstrated other serious or continuing noncompliance with federal, state or local research regulations.

Investigators are required to report **major** protocol deviations that occur only at WVU's research site(s) to the IRB within five (5) working days of their occurrence or within five (5) days of the investigator becoming aware of their occurrence. Investigators are also required to report results of audits or inspections conducted by sponsors or other external entities such as the Food and Drug Administration (FDA), which involve a major protocol violation as defined above.

Investigators are not required to report deviations from other sites unless a WVU investigator serves as the managing investigator for a multi-centered study. The IRB reserves the right to request more frequent reporting and/or the submission of an action plan, depending on the nature of the violations. Major protocol deviations will be reviewed by the IRB Chair or Vice Chair who will determine whether full Committee review is required.

Repetitive deviations may be ruled by the IRB to constitute non-compliance resulting in suspension of IRB approval.

9.4 Reporting & Review

Deviation/Exception Report forms are to be completed for those events that qualify as a protocol deviation or exception. These reports must be filed with the ORIC ***within thirty (30) days of the PI being made aware of the violation.*** The ORIC will forward the report to the IRB Chair or designee for review. An electronic report will be sent back to

the investigator for the study file. The Chair may choose to place any deviation or exception on the agenda of the next convened IRB meeting for discussion. The investigator may be asked to appear at that meeting to answer any questions or clarify issues for the IRB.

 <p>West Virginia University Human Research Protections Program (HRPP) Office of Research Integrity & Compliance STANDARD OPERATING PROCEDURES</p>	<p>Section #: 10 Title: <i>Complaints and Non-Compliance</i> Date: December 10, 2010 Page: Page 154 of 194</p>
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10 Complaints and Non-compliance

As part of its commitment to protecting the rights and welfare of human subjects in research, WVU reviews all complaints 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 subjects research are required to comply with all laws and regulations governing their research activities, as well as with requirements and determinations of the IRB. Study personnel include the principal Investigator and any staff member directly involved with participants or the informed consent process.

The following procedures describe how complaints and allegations of non-compliance are handled by the IRB.

10.1 Definitions

Non-compliance. Non-compliance is defined as failure to comply with any of the regulations and policies described in this document and failure to follow the 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 failure to follow any of the regulations and policies described in this document or failure to follow the determinations of the IRB and which, in the judgment of either the IRB Chair or the convened IRB, increases risks to participants, decreases potential benefits, or compromises the integrity of the Office of Research Integrity and Compliance . Research being conducted without prior IRB approval or participation of subjects in research activities without their prior consent (in studies where consent was not specifically waived by the IRB) is considered serious noncompliance.

Continuing non-compliance. Continuing non-compliance is defined as a pattern of non-compliance that, in the judgment of the IRB Chair or convened IRB, suggests a likelihood that instances of non-compliance will continue without intervention. Continuing non-compliance also includes failure to respond to a request to resolve an episode of non-compliance.

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 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 serious, non-serious, or continuing

10.2 Complaints

The Director will promptly handle (or delegate staff to handle), and, if necessary, investigate all complaints, concerns, and appeals received by the IRB. This includes complaints, concerns, and appeals from investigators, research participants and others.

The identity of any entity bringing a complaint, concern, and/or allegation of non-compliance to the attention of the ORIC shall be kept confidential to the greatest extent possible.

All complaints, written or verbal (including telephone complaints), and regardless of point of origin, are recorded on a complaint form and forwarded to the IRB Chair and ORIC Director.

Upon receipt of the complaint, the 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 3.9.1 will be followed.

If the complaint meets the definition of non-compliance, it will be considered an allegation of non-compliance according to Section 10.3.

If the complaint meets the definition of an unanticipated problem involving risk to subjects or others, it will be handled according to Section 8.

Within 3 business days of receipt of the complaint, the IRB Chair and/or ORIC Director shall generate a letter to acknowledge that the complaint has been received and is being investigated, providing a follow-up contact name.

10.3 Non-compliance

Investigators and their study staff are required to report instances of possible non-compliance. The Principal Investigator is responsible for reporting any possible non-compliance by study personnel to the IRB. Common reports to the IRB that are not serious or continuing are typically protocol deviations. However, any individual or employee may report observed or apparent instances of noncompliance to the WVU 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 institutional review of these reports.

If an individual, whether investigator, study staff or other, is uncertain whether there is cause to report noncompliance, he or she may contact the IRB Chair directly to discuss the situation informally.

Reports of non-compliance must be submitted to the ORIC within 10 working days of discovery of this noncompliance. The report must include a complete description of the noncompliance, the personnel involved and a description of the non-compliance.

Complainants may choose to remain anonymous.

10.3.1 Review of Allegations of Non-compliance

All allegations of non-compliance will be reviewed by the IRB Chair, who will review:

1. All documents relevant to the allegation
2. The last approval letter from the IRB
3. The last approved IRB application and protocol;
4. The last approved consent document
5. The grant, if applicable; and
6. Any other pertinent information (e.g., questionnaires, DSMB reports, etc.).

The IRB Chair will review the allegation and make a determination as to the truthfulness of the allegation. They may request additional information or an audit of the research in question.

When the Chair determines that noncompliance did not occur because the incident was within the limits of an approved protocol for the research involved, the determination is reported in writing to the PI 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 at the outset.

If in the judgment of the IRB Chair, the reported allegation of non-compliance is true, the non-compliance will be processed according to Section 10.3.2 Review of Findings of Non-compliance.

If in the judgment of the IRB Chair, 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 3.9 with subsequent review by the IRB.

The Chair may determine that additional expertise or assistance is required to make these determinations and may form 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 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.

10.3.2 Review of Findings of Non-compliance

Noncompliance is not serious or continuing:

When the Chair determines that the noncompliance occurred, but the noncompliance does not meet definition of serious or continuing noncompliance, the determination is reported in writing to the PI and if applicable the reporting party. The Chair will work with the PI to develop a corrective action plan to prevent future noncompliance. The report of noncompliance and corrective action is reported to the IRB through the “expedited review report”. If however, the PI refuses to cooperate with the corrective action plan, the matter is referred to a convened meeting of the IRB with notification to the IO.

Serious or Continuing Noncompliance

When the Chair determines that noncompliance has occurred and that the noncompliance meets the definition of serious or continuing noncompliance, the report of noncompliance is referred for review by the IRB at the next convened available meeting. However, the Chair may use discretion and call an emergency IRB meeting should the circumstances warrant such an urgent meeting.

All findings of serious or continuing non-compliance referred to the IRB will be reviewed at a convened meeting. All IRB members will receive:

1. All documents relevant to the allegation
2. The last approval letter from the IRB
3. The last approved IRB protocol; and
4. The last approved consent document.

At this stage, the IRB may:

1. Find that there is no issue of non-compliance
2. Find that there is noncompliance that is neither serious nor continuing and an adequate corrective action plan is in place
3. Find that there is serious or continuing non-compliance and approve any changes proposed by the Chair and/or ad hoc committee
4. Find that there may be serious or continuing non-compliance and direct that a formal inquiry (described below) be held; or
5. Request additional information.

10.3.3 Inquiry Procedures

A determination may be made by the IRB that an inquiry is necessary based on several issues that may include but are not limited to:

1. Subjects' complaint(s) that rights were violated;
2. Report(s) that investigator is not following the protocol as approved by the IRB;

3. Unusual and/or unexplained adverse events in a study;
4. Repeated failure of investigator to report required information to the IRB.

A subcommittee is appointed consisting of IRB members, and non-members if appropriate, to ensure fairness and expertise. The subcommittee is given a charge by the IRB, which can include any or all of the following:

1. Review of protocol(s) in question;
2. Review of sponsor audit report of the investigator, if appropriate;
3. Review of any relevant documentation, including consent documents, case report forms, subject's investigational and/or medical files etc., as they relate to the investigator's execution of her/his study involving human subjects;
4. Interview of appropriate personnel if necessary;
5. Preparation of either a written or oral report of the findings, which is presented to the full IRB at its next meeting;
6. Recommend actions if appropriate.

10.3.4 Final Review

The results of the inquiry will be reviewed at a convened IRB meeting where the IRB will receive a report from the subcommittee. If the results of the inquiry substantiate the finding of serious or continuing non-compliance, the IRB's possible actions could include, but are not limited to:

1. Request a correction action plan from the investigator
2. Verification that participant selection is appropriate and observation of the actual informed consent
3. An increase in data and safety monitoring of the research activity
4. Request a directed audit of targeted areas of concern
5. Request a status report after each participant receives intervention
6. Modify the continuing review cycle
7. Request additional Investigator and staff education
8. Notify current subjects, if the information about the non-compliance might affect their willingness to continue participation
9. Require modification of the protocol
10. Require modification of the information disclosed during the consent process
11. Require current participants to re-consent to participation
12. Suspend the study (See below); or
13. Terminate the study (See below)

In cases where the IRB determines that the event of noncompliance also meets the definition of unanticipated problem involving risks to subjects or others, the policy and procedure for review of such events will also be followed.

The investigator is informed of the IRB determination and the basis for the determination in writing and is given a chance to respond. 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 11.

10.4 VA Research

Under VHA Handbook 1058.01, The IRB must review any report of apparent serious or continuing noncompliance received from the VA at its next convened meeting.

Should the IRB determine that the reported incident constitutes serious noncompliance or continuing noncompliance, the IRB Chair, or designee must report the determination directly (without intermediaries) to the facility Director within 5 business days after the determination.

The IRB Chair's report must be made in writing, with a simultaneous copy to the ACOS for Research, the R&D Committee, and any other relevant research review committee.

An initial report of an IRB determination that serious noncompliance or continuing noncompliance occurred is required, even where the determination is preliminary or disposition of the matter has not been resolved at the time of the report.

NOTE: The IRB must reach a determination that serious or continuing noncompliance did (or did not) occur within 30-45 days after receiving a report of apparent noncompliance. Remedial actions involving a specific study or research team must be completed within 90-120 days after the IRB's determination. Remedial actions involving programmatic noncompliance must be completed within 120-180 days after the IRB's determination, unless remediation requires substantial renovation, fiscal expenditure, hiring, legal negotiations, etc.



**Human Research Protections Program
(HRPP)**

Office of Research Integrity & Compliance

STANDARD OPERATING PROCEDURES

Section #: 11

Title: *Reporting to Regulatory
Agencies and Institutional
Officials*

Date: December 10, 2010

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11 Reporting to Regulatory Agencies and Institutional Officials

Federal regulations require prompt reporting to appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval. The WVU HRPP will comply with this requirement and the following procedures describe how these reports are handled.

11.1 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 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 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 principal investigator on the protocol
 - 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, 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 and the IO review the letter and modify the letter/report as needed
 4. The Institutional Official is the signatory for all correspondence from the facility.
 5. The 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 federalwide assurance
 - 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 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. For VA research, the LAJVAMC Research Office for appropriate reporting under VA regulations.
 - e. Principal investigator
 - f. Sponsor, if the study is sponsored
 - g. Contract research organization, if the study is overseen by a contract research organization
 - h. Chairman or supervisor of the principal investigator
 - i. The Privacy Officer of a covered entity, if the event involved unauthorized use, loss, or disclosure of individually-identifiable patient information from that covered entity
 - j. The Information Security Officer of an organization if the event involved violations of information security requirements of that organization
 - k. Office of Risk Management, if appropriate

- I. Others as deemed appropriate by the Institutional Official

The Director ensures that all steps of this policy are completed within 10 working days of the determination. For more serious actions, the Director will expedite reporting.

 <p>West Virginia University Human Research Protections Program (HRPP) Office of Research Integrity & Compliance STANDARD OPERATING PROCEDURES</p>	<p>Section #: 12 Title: <i>Investigator Responsibilities</i> Date: December 10, 2010 Page: Page 165 of 194</p>
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12 Investigator Responsibilities

Principal Investigators are ultimately responsible for the conduct of research. Principal Investigators may delegate research responsibility. However, investigators must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility.

The following procedures describe the investigator responsibilities in the conduct of research involving human participants.

12.1 Investigators

Principal Investigators

At WVU only **faculty or staff members with Organization-paid appointments** may serve as the Principal Investigator or as the faculty sponsor on a research project involving human subjects.

At the **LAJVAMC**, a Principal Investigator and/or an investigator must be either compensated by VA, be appointed to work without compensation (WOC), or may be an employee assigned to VA through the Intergovernmental Personnel Act (IPA) of 1970.

Adjunct faculty of the Organization and any investigator whose status is considered to be “in training” (i.e. students and medical residents) may generally not serve as a Principal Investigator but may serve as a co-investigator. Exceptions for adjunct faculty who wish to serve as a principal investigator are predicated on approval by the relevant Department Chair.

The IRB recognizes one Principal Investigator (PI) for each study. The PI has ultimate responsibility for the research activities.

Protocols that require skills beyond those held by the Principal Investigator must be modified to meet the investigator's skills or have one or more additional qualified faculty as Co-investigator(s).

Student Investigators

Students may not serve as Principal Investigators. They must have a faculty sponsor who fulfills the PI eligibility criteria and who will serve as Principal Investigator and faculty advisor on the study.

Research Team

The PI and other individuals, also known as key personnel, who contribute to the scientific development or execution of a project in a substantive, measurable way, whether or not they receive salaries or compensation under the protocol make up the research team. The research team also consists of individuals who intervene or interact directly with human subjects (including the recruitment or consenting thereof), or who analyze identifiable data and/or tissue derived from humans for the purposes of the activity in question.

12.2 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. 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. A process to ensure that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions;
 - f. Availability of medical or psychological resources that subjects might require as a consequence of the research.
4. 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 West Virginia and the policies of West Virginia University Hospitals;
5. Assure that all key personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principals upon which they are based;
6. Protect the rights and welfare of prospective subjects;

7. Ensure that 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;
8. Recruit subjects in a fair and equitable manner;
9. Obtain and document informed consent as required by the IRB and ensuring that no human subject is involved in the research prior to obtaining their consent;
10. Have plans to monitor the data collected for the safety of research subjects;
11. Protect the privacy of subjects and maintain the confidentiality of data;
12. 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, include additional safeguards in the study to protect the rights and welfare of these subjects;
13. Have a procedure to receive complaints or requests for additional information from subjects and respond appropriately;
14. Ensure that pertinent laws, regulations, and institution procedures and guidelines are observed by participating investigators and research staff;
15. Ensure that all research involving human subjects receives IRB review and approval in writing before commencement of the research;
16. Comply with all IRB decisions, conditions, and requirements;
17. Ensure that protocols receive timely continuing IRB review and approval;
18. Report unanticipated problems involving risk to subjects or other and any other reportable events to the IRB (see Section 8);
19. Obtain IRB review and approval in writing before changes are made to approved protocols or consent forms;
20. Seek IRB assistance when in doubt about whether proposed research requires IRB review.

12.3 Training / Ongoing Education of Investigators and Research Team

As stated above, one component of a comprehensive HRPP is an education program for all individuals involved with research subjects. WVU 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 institutional requirements for the protection of human subjects.

12.3.1 Orientation

All Principal Investigators and members of their research team (also known as “key personnel”) must review core training documentation including the “WVU Standard

Operating Policies and Procedures for Human Research Protection,” the “Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research” and the Collaborative Institutional Training Initiative (CITI) Program appropriate to the research being conducted.

12.3.2 Initial Education

The PI and key investigators must complete the WVU Required Core Modules in CITI Course in the Protection of Human Research Subjects.

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

While research protocols and applications for continuing review will not be accepted and reviewed until all co-investigators and members of the research team have completed the initial education requirement.

Waiver of Initial Education

If investigators or members of their research team can verify that they have successfully completed human subjects research training equivalent to that required by WVU, they may request a waiver of the requirement for Initial Education. However, all investigators or members of their research team must complete the requirements of Continuing Education. However, proof of equivalency is required and needs to be submitted with the protocol

12.3.3 Continuing Education and Recertification

All investigators and members of their research teams must meet WVU 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 review of appropriate refresher modules at the CITI web-based training site. Other training may be acceptable. In these cases the researcher should check with the ORIC for a determination.

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

Investigators who are also IRB Chairs, IRB members, or ORIC staff will satisfy the training requirements for IRB members and staff described in this policy under Section 2.12.

12.4 Investigator Concerns

Investigators who have concerns or suggestions regarding WVU’s Office of Research Integrity and Compliance should convey them to the Institutional Official or other responsible parties (e.g. college dean, departmental Chair) regarding the issue, when appropriate. The Institutional Official will research the issue, and when deemed necessary, 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 relevant IRB and/or the ORIC Director will be available to address investigators' questions, concerns and suggestions.



**Human Research Protections Program
(HRPP)**

Office of Research Integrity & Compliance

STANDARD OPERATING PROCEDURES

Section #: 13

Title: *Sponsored Research*

Date: December 10, 2010

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13 Sponsored Research

It is WVU policy that any sponsored research conducted under the auspices of the University 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.

13.1 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 through a grant or contract that involves a specified statement of work (e.g., the research proposal) with a related transfer of value to the sponsor, including clinical trials involving investigational drugs, devices or biologics.

13.2 Responsibility

- 1) Sponsor contracts that are reviewed by the WVU Office of Sponsored Programs:
 - a) The Office of Sponsored Programs will review contracts and the IRB and Office of Sponsored Programs will share contract and study information as necessary for each sponsored protocol to ensure that protocol, consent, and contract language are consistent.
- 2) Sponsor contract NOT reviewed by the Office of Sponsored Programs:
 - a) When a contract is not reviewed by Sponsored Programs, but is reviewed by another entity in which the investigator reports, the IRB application requests a copy of the contract to ensure that the protocol, consent and contract is consistent.
- 3) Contracts will be reviewed for the following by both the Office of Sponsored Programs and the IRB:
 - a) All sponsor contracts will indicate that WVU will follow the protocol, applicable regulations and its ethical standards.
 - b) All sponsor contracts will define who will be responsible for research related injuries.

- c) If the sponsor will monitor the conduct of the research, the contract will be required to state that if the study monitor uncovers information that could affect the safety of participants or their willingness to continue participation, influence the conduct of the study, or alter the IRB's approval to continue the study, the sponsor will make sure that the information is communicated to the IRB.
- d) If the sponsor discovers results that could affect the safety or medical care, the sponsor will make sure the IRB is notified.
- e) Payment in exchange for referrals of prospective participants from researchers (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.
- f) Submit any information from the sponsor regarding participant safety to the IRB for review regardless of the status of the protocol, i.e., open or closed.

 <p>West Virginia University Human Research Protections Program (HRPP) Office of Research Integrity & Compliance STANDARD OPERATING PROCEDURES</p>	<p>Section #: 14 Title: <i>Conflict of Interest in Research</i> Date: December 10, 2010 Page: Page 172 of 194</p>
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14 Conflict of Interest in Research

It is WVU policy to preserve public trust in the integrity and quality of research at the University by minimizing actual or perceived conflict of interest in the conduct of research.

The following describe the procedures by which this responsibility is carried out.

14.1 Definitions

Conflict of Interest. A conflict of interest (COI) occurs when any financial arrangement, situation or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results or reporting of research activities or findings.

Ownership interest. Ownership interest means any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a non-publicly traded corporation), or any equity interest in a publicly traded corporation during the time the investigator is carrying out the study and for 1 year following completion of the study.

Compensation. Compensation means payments made by an organization to the investigator or the institution exclusive of the costs of conducting the research during the time the investigator is carrying out the study and for 1 year following the completion of the study. This includes, but is not limited to:

- Income from seminars, lectures or teaching engagements
- Income from service on advisory committees or review panels
- Grants to fund ongoing research
- Compensation in the form of equipment
- Retainers for ongoing consultation

Patent. A patent is an official written document securing to an inventor for a term of years the exclusive right to make, use, or sell an invention.

Royalty. A royalty is compensation for an invention.

Immediate Family Member. Immediate family member: having a relationship to a person (whether by blood, law, or marriage) as a spouse, parent, child, grandparent, grandchild, stepchild, or sibling.

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

Significant Financial Interest. Significant Financial Interest includes:

- Ownership interest, stock options, or other financial interest related to the research unless it meets four tests:
 - Less than \$10,000 when aggregated for the immediate family.
 - Publicly traded on a stock exchange.
 - Value will not be affected by the outcome of the research.
 - Less than 5% interest in any one single entity.
- Compensation related to the research unless it meets two tests:
 - Less than \$10,000 in the past year when aggregated for the immediate family.
 - Amount will not be affected by the outcome of the research.
- Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright or licensing agreement.
- Board or executive relationship related to the research, regardless of compensation.

Non-financial Conflict of Interest. Non-financial conflict of interest may exist when an individual serves dual roles, such as health care provider and investigator. Other interests such as publication, promotion or tenure, can also become conflicts of interest that may affect an individual's judgment. Membership in oversight committees such as the IRB as well as positions of authority may pose potential conflicts of interest. Any position that includes responsibilities for the review and approval of research projects or contracts other than his/her own may potentially affect the design of, decisions made and/or action taken surrounding a specific study.

Key Personnel. Key research personnel are those individuals who: 1) obtain consent from human subjects; 2) recruit human subjects; or 3) evaluate the response of human subjects.

14.2 Individual Conflicts of Interest

These procedures apply to both financial and non-financial conflicts of interest and are guided by Code of Federal Regulations (Title 42 of the Code of Federal Regulations (CFR) Part 50 Subpart F) that promotes objectivity in research to ensure conflict of interests do not adversely affect the protection of participants or the credibility of the WVU HRPP.

For clinical studies involving the use of new human drugs and biological products or medical devices, certifications and disclosure requirements are defined in Food and Drug Administration (FDA) regulations, Title 21 CFR Part 54.

In the environment of research, openness and honesty are indicators of integrity and responsibility, characteristics that promote quality research and can only strengthen the research process. Therefore, conflicts of interest should be eliminated when possible and effectively disclosed and managed when they cannot be eliminated.

14.2.1 Procedures

14.2.1.1 Disclosure of Investigator COI

The IRB application form links investigators to protocol-specific questions regarding conflict of interest for investigators, key personnel and their immediate families of:

- Significant financial interest (as defined above) in the organization sponsoring the research or in a competing organization.
- Any financial interest that requires disclosure to the sponsor or funding source
- Any financial interest in the research with value that cannot be readily determined.
- Any other financial interest that the investigator believes may interfere with his or her ability to protect participants.
- Any non-financial interest (as defined above) that the investigator believes may interfere with his or her ability to protect participants.
- If the investigator or his/her family has a financial interest they will check yes on the IRB application and then be redirected to the COI website.

14.2.1.2 Evaluation of COI

At initial review of the research protocol and COI disclosure, the IRB also determines the following:

- Whether the conflict, financial or non-financial, affects the protections of research participants,
- Whether a conflicting interest might adversely affect the credibility of the HRPP thus creating the appearance of conflicts of interest.

Points to consider are:

- How is the research supported or financed,
- By whom the study is designed,
- Will the institution receive any compensation, and if the institution is an appropriate site for the research.

14.2.1.3 Management of COI

The IRB will determine if the rights and welfare of human research participants will be better protected by any or a combination of the following:

1. Disclosure to subjects through the consent process
2. Modification of the research protocol or safety monitoring plan
3. Monitoring of research by independent reviewers
4. Disqualification of the conflicted party from participation in all or a portion of the research
5. Appointment of a non-conflicted Principal Investigator
6. Divestiture of significant financial interests
7. Severance of relationships that create actual or potential conflicts.
8. Prohibition of the conduct of the research at the University

14.3 Recruitment Incentives

Payment arrangements among sponsors, organizations, investigators, and those referring research participants may place participants at risk of coercion or undue influence or cause inequitable selection. Payment in exchange for referrals of prospective participants from researchers (physicians) (“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.

Note: For faculty and staff employed by the LAJVAMC: Questions regarding finder's fees and incentives involving VA studies should be directed to the LAJVAMC Research Office or VA regional counsel.

14.4 Institutional Conflict Of Interest

These procedures apply to all human subjects research conducted at WVU. This policy applies to investigators, IRB members and staff, and institutional officials.

The policy of WVU is to ensure that the welfare of human subjects and the integrity of research will not be compromised, or appear to be compromised, by competing institutional interests or obligations. Although Organization policy has separated technology transfer functions from research administration, circumstances may exist in which separation of function is not sufficient to avoid the appearance of institutional conflict of interest.

The Institutional Conflict of Interest policy was approved December 9, 2010 for implementation in the 2011/2012 academic year.

14.4.1 Responsibilities

The Conflict of Interest in Research Committee (CIRC) will be responsible for evaluating potential institutional conflict of interest and will take actions as required to avoid, or to

appropriately manage, apparent institutional COI. These actions may involve referral to appropriate advisors outside the facility or obtaining advisement from the WVU General Counsel. If used, outside advisors will be individuals who have sufficient seniority, expertise, and independence to evaluate the competing interests at stake and to make credible and effective recommendations. All outside advisors will be independent of the management of oversight for the HRPP within the institution. The utilization of outside advisors will increase the transparency of the deliberations and enhance the credibility of determinations. After reviewing a significant financial interest in research, the CIRC will communicate its conclusions, along with any management arrangements to be imposed, to the IRB. All relevant conflicts will be disclosed to research participants in a form to be determined by the IRB. The CIRC also will communicate conclusions and COI management strategies to the Institutional Official and the PI.

14.4.2 Identification of Institutional Conflict of Interest

14.4.3 Management of Conflict of Interest

As part of its review of institutional COI, the CIRC will ask if any related research involves human subjects. If yes, any conflict management plan which is developed will be forwarded to the IRB.

14.4.3.1 Assumption of conflict of interest

If the University retains a significant financial interest, or if an institutional official with direct responsibility for the HRPP holds a significant financial interest in the invention, then the CIRC must assess the potential conflict of interest and weigh the magnitude of any risk to human participants. When reviewing potential institutional conflict of interest, the CIRC will assume an inclination against the conduct of human participants research at, or under the auspices, of the institution where a COI appear to exist. However, the assumption may be overturned by the Committee when the circumstances are compelling and the Committee has approved an effective conflict management plan.

14.4.3.2 Decision making

A key aspect in decision-making is to analyze when it would be appropriate and in the public interest to accept and manage a COI, rather than require that the COI be eliminated. In some cases, the benefits of conducting a proposed research activity at the institution will be potentially high, and the risks will be low. In other cases, the scientific advantages of conducting the research may be speculative and the risks may be great. In these latter instances, the conflict should be avoided by disapproving the research application.

14.4.3.3 Evaluation of risk

Each case should be evaluated based upon the following:

1. The nature of the science;
2. The nature of the interest;

3. How closely the interest is related to the research;
4. The degree of risk that the research poses to human participants; and
5. The degree to which the interest may be affected by the research.

The CIRC will consider whether the institution is uniquely qualified, by virtue of its attributes (e.g., special facilities or equipment, unique patient population) and the experience and expertise of its investigators, to conduct the research and safeguard the welfare of the human subjects involved.

14.4.3.4 Potential actions

Potential actions to be considered to better protect subjects are any (or a combination) of the following:

- a. Public disclosure of the financial interest;
- b. Not conducting proposed research at that institution, or halting it if it has commenced;
- c. Reducing or otherwise modifying the financial (equity or royalty) stake involved;
- d. Increasing the segregation between the decision-making regarding the financial and the research activities;
- e. Requiring an independent data and safety monitoring committee or similar monitoring body;
- f. Modifying of role(s) of particular research staff or changes in location for certain research activities, e.g., a change of the person who seeks consent, or a change in investigator; or
- g. Establishing a research monitoring process, so that the research can be closely scrutinized to ensure that potential conflicts do not undermine the integrity of the work and of the University.

 <p>West Virginia University Human Research Protections Program (HRPP) Office of Research Integrity & Compliance STANDARD OPERATING PROCEDURES</p>	<p>Section #: 15 Title: <i>Participant Outreach</i> Date: December 10, 2010 Page: Page 178 of 194</p>
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15 Participant Outreach

WVU 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 WVU.

The following procedures describe how WVU fulfills that responsibility.

15.1 Responsibility

It is the responsibility of the IRB manager to implement the procedures outlined below.

15.2 Outreach Resources and Educational Materials

1. The ORIC dedicates a section of its website to research participants entitled "Participant Outreach Corner". This website includes resources, such as Frequently Asked Questions (FAQs), WVU designed brochures (Volunteering in Research), and a listing of relevant research-related links.
2. WVU periodically provides PowerPoint presentations related to research to community organization.
3. WVU provides several relevant links to the Office for Human Research Protections (OHRP) campaign to inform the general public about research participation: <http://www.hhs.gov/ohrp/outreach/>. Participants, prospective participants, and community members may access this information from the "Participant Outreach Corner" to increase public awareness and educate potential research participants.

15.3 Evaluation

WVU periodically evaluates its outreach activities and makes changes when appropriate. These evaluations take place in an informal, ongoing manner. All IRB staff, members and Chairs/Co-Chairs will report both positive and negative feedback about all HRPP outreach activities to the IRB Manager. He/she will then track the input and any changes made to improve outreach activities. He/she will summarize that material annually. In order to formally evaluate its outreach activities, the IRB Manager will determine:

1. The specific community outreach activities being used;
2. Whether or not these community outreach activities have an evaluative component, and if so what, if any, changes in the outreach activities have resulted from these evaluations.

The IRB Office will administer surveys annually to determine the adequacy of outreach activities. The survey will assess:

1. The scope, the content and the adequacy of outreach activities and resources.
2. Whether the research community is using the ORIC website resource *Participant Outreach Corner*.
3. Whether the research community is using other educational materials to inform prospective participants about their rights and welfare as research participants.
4. Whether additional resources are needed to improve participant outreach activities.

The results of the survey 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.

 <p>West Virginia University Human Research Protections Program (HRPP) Office of Research Integrity & Compliance STANDARD OPERATING PROCEDURES</p>	<p>Section #: 16 Title: <i>Health Insurance Portability and Accountability Act (HIPAA)</i> Date: December 10, 2010 Page: Page 181 of 194</p>
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16 Health Insurance Portability and Accountability Act (HIPAA)

Protected Health Information obtained by WVU may not be used internally or disclosed to any outside person or organization for research purposes without prior approval of the IRB. WVU researchers must also abide by all corporate HIPAA policies regarding HIPAA privacy and security.

The following describe the procedures for conducting research at WVU in accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

16.1 Definitions

Access. Access is the mechanism of obtaining or using information electronically, on paper, or other medium for the purpose of performing an official function.

Authorization. An authorization is a detailed document that gives covered entities permission to use protected health information for specified purposes, which are generally other than treatment, payment, or health care operations, or to disclose protected health information to a third party specified by the individual.

Covered entity. Covered entity is the term applied to institutions that must comply with the Privacy Rule. These include:

- Health plans
- Health care clearinghouses
- Health care providers who conduct certain financial and administrative transactions electronically. These electronic transactions are those for which standards have been adopted by the Secretary under HIPAA, such as electronic billing and fund transfers.

Common Rule. Common Rule is a federal Policy on human subject protection that provides for the primary source of regulation of research.

De-Identified Information. De-Identified Information is health information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual. If information is de-identified it no longer is subject to the Privacy Rule and exempt from HIPAA.

Deletion. Deletion is the removal, erasing, or expunging of information or data from a record.

Disclosure. Disclosure is the release, transfer, provision of access to, or divulging in any other manner information outside of the covered entity.

Health Information. Health Information is any information created or received by a health care provider or health plan that 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 payment for the provision of health care to an individual.

Identifiable Health Information. Identifiable Health Information is a subset of health information including demographic information collected from an individual.

Limited Data Set. Limited Data Set is protected health information that excludes specific direct identifiers of the individual or of relatives, employees or household members of an individual. A limited data set can only be used for the purposes of research, public health, or healthcare operations, and disclosed for the purpose of research.

Minimum Necessary. Minimum Necessary refers to the principle that any access should be limited to the minimum amount of information needed to accomplish the intended purpose of the use or disclosure.

Privacy Board . Privacy Board is the term used to describe a board comprised of members of varying backgrounds and appropriate professional competencies, as necessary, to review individual's private rights. It is an alternative to an IRB for privacy issues only. It cannot replace the IRB for Common Rule purposes.

Privacy Act. Privacy Act is an act that provides for the confidentiality of individually identified and retrieved information about living individuals that is maintained in a system of records and permits the disclosure of records only when specifically authorized by the statute. The Act provides that the collection of information about individuals is limited to that which is legally authorized, relevant, and necessary.

Privacy Rule. Privacy Rule provides guidance on the use of protected health information in the conduct of research. It imposes requirements on those involved in research, both individuals and institutions. Privacy refers to a person's desire to control the access of others to themselves. The evaluation of privacy involves consideration of how the investigator will access information from or about participants. The IRB members should know strategies to protect privacy interests relating to contact with potential participants, and access to private information.

Protected Health Information. Protected Health Information is individually identifiable health information transmitted or maintained electronically or in any other form or medium, except for education records or employment records, as excluded in the Privacy Rule.

Preparatory Research. Preparatory Research is the method applied to developing or designing a research study.

Waiver of Authorization. Waiver of Authorization is a means of requesting approval from an IRB or Privacy Board rather than asking each research subject for an authorization to access protected health information.

16.2 Historical Background

The *Health Insurance Portability and Accountability Act of 1996* (HIPAA) required the creation of a Privacy Rule for identifiable health information. The resulting Privacy Rule, finalized in August 2002, set a compliance date of April 14, 2003. While the main impact of the Privacy Rule will be on the routine provision of and billing for health care, the Rule will also affect the conduct and oversight of research. Researchers, IRB staff and members as well as research administration must be aware of these changes.

16.3 Effects of HIPAA on Research

The final Privacy Rule published on August 14, 2002 included a number of changes in how the Rule applies to research. See the NIH HIPAA Privacy Rule Booklet for Research and the NIH fact sheet on Institutional Review Boards and HIPAA for more information on how HIPAA applies to research. See also *Impact of the Privacy Rule on Academic Research*, a white paper published by the American Council on Education.

The Privacy Rule does not make any changes to the Common Rule. However, it does contain several provisions that resemble provisions of the Common Rule and does make reference to those provisions. The Common Rule contains specific requirements for the composition of an IRB and the Privacy Rule contains specific requirements for a Privacy Board. The composition of a Privacy Board is similar to that of an IRB.

WVU is a covered entity under HIPAA. Researchers who are working with “Protected Health Information” (PHI) will be required to comply with the rules on HIPAA. The WVU IRB acts as the Institution’s Privacy Board.

The Privacy Rule permits covered entities to use or disclose protected health information for research purposes when the individual who is the subject of the information authorizes the use or disclosure. For clinical trials, authorization must be sought in addition to informed consent. Authorization must also be sought for other research uses or disclosures of protected health information that do not qualify for an IRB waiver of authorization (discussed below).

The Privacy Rule has several special provisions that apply to research authorizations for uses and disclosures of PHI for research purposes. These requirements are as follows:

1. An authorization for a research purpose may state that the authorization does not expire, that there is no expiration date or event, or that the authorization continues until the end of the research study; and
2. An authorization for the use or disclosure of protected health information for research may be combined with a consent to participate in the research, or with any other legal permission related to the research study (except for research

involving the use or disclosure of psychotherapy notes, which must be authorized separately); and

3. Research authorization forms must be filled out completely and accurately by the investigator, to ensure that all parties who require access to protected health information for the research (including sponsors, CROs, DSMBs, IRBs, etc.) are identified in the form and may receive the information. The IRB combined authorization/consent form should be completed by the investigator and submitted to the WVU IRB for review and approval.

16.4 Research under HIPAA

HIPAA defines research as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." This definition is identical with the one used in the "Common Rule", separate federal legislation designed to protect human subjects involved in research. HIPAA describes privacy standards for protecting PHI and so only applies to research that involves humans' (not animals') health information.

16.4.1 Waiver of Authorization for Use or Disclosure of Protected Health Information in Research

Under the Privacy Rule, covered entities are permitted to use and disclose protected health information for research with individual authorization, or without individual authorization under limited circumstances. A covered entity may use or disclose protected health information for research when presented with documentation that an IRB has granted a waiver of authorization [see 45 CFR 164.512(i)(1)(i)]. This provision of the Privacy Rule might be used, for example, to conduct records research, epidemiological studies, or other research where de-identified data is unavailable or not suited to the research purpose.

The waiver documentation presented to the covered entity must include the following:

1. Identification of the IRB or Privacy Board and the date on which the alteration or waiver of authorization was approved;
2. A statement that the IRB or Privacy Board has determined that the alteration or waiver of authorization, in whole or in part, satisfies the three criteria in the Rule;
3. A brief description of the protected health information for which use or access has been determined to be necessary by the IRB or Privacy Board;
4. A statement that the alteration or waiver of authorization has been reviewed and approved under either normal or expedited review procedures; and
5. The signature of the chair or other member, as designated by the chair, of the IRB or the Privacy Board, as applicable.

The following criteria must be satisfied for the IRB to approve a waiver of authorization under the Privacy Rule:

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:

1. an adequate plan to protect the identifiers from improper use and disclosure;
2. an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
3. adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;
4. The research could not practicably be conducted without the waiver or alteration; and
5. The research could not practicably be conducted without access to and use of the protected health information.

16.4.2 Review Preparatory to Research

The Privacy Rule permits a covered entity to use or disclose protected health information to a researcher without authorization or waiver for the limited purpose of a “review preparatory to research.” Such reviews may be used to prepare a research protocol, or to determine whether a research site has a sufficient population of potential research subjects. Prior to permitting the researcher to access the protected health information, the covered entity must obtain representations from the researcher that the use or disclosure of the protected health information is solely to prepare a research protocol or for similar purposes preparatory to research, that the researcher will not remove any protected health information from the covered entity, and that protected health information for which access is sought is necessary for the research purpose. Researchers should consult the covered entity regarding any forms or applications necessary to conduct a review preparatory to research.

Researchers conducting a review preparatory to research may not record information in identifiable form, may not use data obtained in review as part of the study (report as “pre” data in a pre/post design protocol) nor may they use the information that they receive to contact potential subjects, unless the investigator is also the subject’s treating physician. Because the Privacy Rule permits a covered entity to disclose protected health information to the individual who is the subject of the information, covered health care providers and patients may continue to discuss the option of enrolling in a clinical trial without patient authorization. Even when permitted by the Privacy Rule, however, any use of patient information for recruitment must comply with IRB recruitment policies (see discussion below).

1. All human subjects research requires IRB review to determine either a) exempt status or b) need for further review.

2. Reviews preparatory to research that are permitted under HIPAA may or may not be human subjects research depending on the investigation being conducted.
 - a. A database containing PHI can only be accessed by a clinician when there is a clinical need to access the chart. It may not be accessed for research except to extract aggregate data, not individual PHI. No individual PHI may be reviewed or recorded.
 - b. If the research involves a de-identified data set, defined as removing the following identifiers, then a de-identified data set certification form must be completed and submitted for administrative review and certified prior to accessing the data set. This activity also requires an IRB determined exemption from review:
 1. Names
 2. Geographic info. (city, state, and zip)
 3. Elements of Dates (except years)
 4. Telephone #s
 5. Fax #s
 6. E-mail address
 7. Social Security#
 8. Medical Record, prescription #s
 9. Health Plan Beneficiary #s
 10. Account #s
 11. Certificate /License #s
 12. VIN and Serial #s, license plate #s.
 13. Device identifiers, serial #s
 14. Web URLs
 15. IP address #s
 16. Biometric identifiers (finger prints)
 17. Full face, comparable photo images
 18. Unique identifying #s

IRB Privacy Board review and approval is required prior to initiating this research. Investigators are not authorized to contact potential research subjects identified in reviews preparatory to research unless they are directly responsible for care of the potential subject and entitled to PHI as a result of that duty.

Investigators who have previously obtained full consent and authorization to contact a research subject as a result of a previously approved research project, may contact his or her former research subjects provided that the subject agreed to be contacted for information on future research conducted by the same principal investigator or co-investigator (s).

16.4.3 Research on Protected Health Information of Decedents

The protections of the Common Rule apply only to living human beings; by contrast, the Privacy Rule also protects the identifiable health information of deceased persons (“decedents”). The Privacy Rule contains an exception to the authorization requirement for research that involves the protected health information of decedents. A covered entity may use or disclose decedents’ protected health information for research if the

entity obtains representations from the researcher that the use or disclosure being sought is solely for research on the protected health information of decedents, that the protected health information being sought is necessary for the research, and, at the request of the covered entity, documentation of the death of the individuals about whom information is being sought. Researchers should submit the applicable IRB form for IRB approval when they intend to conduct research involving decedents' protected health information.

16.4.4 Limited Data Sets with a Data Use Agreement

When a researcher does not need direct identifiers for a study but does require certain data elements that are not permitted in de-identified data, the Privacy Rule permits a covered entity to disclose a "limited data set" to the researcher without authorization or waiver, provided that the researcher has signed a data use agreement. The limited data set is still considered to be protected health information, but it must exclude only specified direct identifiers of the individual or of relatives, employers, or household members of the individual.

If the research involves a limited data set, it involves removing the following 15 identifiers:

1. Names
2. Postal address info. (if other than city, state and zip)
3. Telephone and fax #s
4. Email addresses
5. Social Security #s
6. Medical record, prescription numbers
7. Health plan beneficiary #s
8. Account #s
9. Certificate/license #s
10. Vin and serial #s, license plate #s
11. Device identifiers, serial #s
12. Web URLs
13. IP address #s
14. Biometric identifiers (finger prints)
15. Full face, comparable photo images

The Privacy Rule requires that the data use agreement used in conjunction with the limited data set contain provisions that:

1. Establish the permitted uses and disclosures of the limited data set by the recipient, consistent with the purposes of the research, and which may not include any use or disclosure that would violate the Rule if done by the covered entity;
2. Limit who can use or receive the data; and
3. Require the recipient to agree to the following:
 - a. Not to use or disclose the information other than as permitted by the data use agreement or as otherwise required by law;

- b. Use appropriate safeguards to prevent the use or disclosure of the information other than as provided for in the data use agreement;
 - c. Report to the covered entity any use or disclosure of the information not provided for by the data use agreement of which the recipient becomes aware;
 - d. Ensure that any agents, including a subcontractor, to whom the recipient provides the limited data set agrees to the same restrictions and conditions that apply to the recipient with respect to the limited data set; and
 - e. Not to identify the information or contact the individual.
4. Researchers who will be receiving limited data sets must submit a signed copy of the covered entity's data use agreement to the ORIC IRB for approval, prior to initiating the research.

16.4.5 Transition Provisions

The Privacy Rule contains certain grandfathering provisions that permit a covered entity to use and disclose protected health information for research after the Rule's compliance date of April 14, 2003, if the researcher obtained any one of the following prior to the compliance date:

1. An authorization or other express legal permission from an individual to use or disclose protected health information for the research;
2. The informed consent of the individual to participate in the research; or
3. An IRB waiver of informed consent for the research.

Even if informed consent or other express legal permission was obtained prior to the compliance date, if new subjects are enrolled or existing subjects are re-consented after the compliance date, the covered entity must obtain the individual's authorization. For example, if there was a temporary waiver of informed consent for emergency research under the FDA's human subject protection regulations, and informed consent was later sought after the compliance date, individual authorization must be sought at the same time.

The transition provisions apply to both uses and disclosures of protected health information for specific research protocols and uses or disclosures to databases or repositories maintained for future research.

16.5 HIPAA and Documentation Requirements

HIPAA documents include an authorization form, a waiver of authorization form, and a de-identification form which is required only for databases that are not generally known to be de-identified and that are widely available for public consumption from the government. One of these documents must be used whenever PHI is utilized in the research.

16.6 Patient Rights and Research

Under HIPAA, patients have certain rights. Those that may affect research include the right to receive a Notice of Privacy Practices, the right to access, inspect, and receive a copy of one's own PHI, the right to request an amendment to one's own PHI, and the right to an accounting of certain disclosures of PHI that occur outside the scope of treatment, payment and health care operations that have not been authorized.

16.7 HIPAA and Existing Studies

Any research subject enrolled in a study that uses PHI from a covered entity must sign a HIPAA-compliant authorization form. This form is in addition to the existing Informed Consent document, and is federally required. Generally, the Informed Consent document may be combined with a HIPAA authorization.

16.8 Waivers to HIPAA Consent Form

In some cases the WVU IRB may approve a waiver to use of the HIPAA authorization form. This may occur when the IRB finds that the research could not be practically done without the waiver, and not without access to and use of the PHI, and that disclosure poses minimal risk to privacy.

 <p>West Virginia University Human Research Protections Program (HRPP) Office of Research Integrity & Compliance STANDARD OPERATING PROCEDURES</p>	<p>Section #: 17 Title: <i>Special Topics</i> Date: December 10, 2010 Page: Page 190 of 194</p>
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17 Special Topics

17.1 Certificate of Confidentiality (CoC)

Certificates of Confidentiality are issued by the federal government to protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. CoCs 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.

The certificate goes beyond the consent form in ensuring confidentiality and anonymity. Without the certificate, researchers can be required by a court-ordered subpoena to disclose research results (usually as part of a criminal investigation of the subjects).

Any research project that collects personally identifiable, sensitive information and that has been approved by an IRB is eligible for a Certificate. Federal funding is not a prerequisite for a Certificate.

17.1.1 Statutory Basis for Protection

Protection against compelled disclosure of identifying information about subjects of biomedical, behavioral, clinical, and other research is provided by the Public Health Service Act §301(d), 42 U.S.C. §241(d):

"The Secretary may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, including research on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals."

17.1.2 Usage

Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality 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 Certificate of Confidentiality. Research can be considered "sensitive" if it involves the collection of:

1. information about sexual attitudes, preferences, practices;
2. information about personal use of alcohol, drugs, or other addictive products;
3. information about illegal conduct;
4. information that could damage an individual's financial standing, employability, or reputation within the community;
5. information in a subject's medical record that could lead to social stigmatization or discrimination; or
6. information about a subject's psychological well-being or mental health.

This list is not exhaustive. Researchers contemplating research on a topic that might qualify as sensitive should contact the ORIC for help in applying for a certificate.

In the informed consent form, investigators should tell research subjects that a Certificate 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 Certificate is in effect.

17.1.3 Limitations

The protection offered by a Certificate of Confidentiality is not absolute. A Certificate protects research subjects only from legally compelled disclosure of their identity. It does **not** restrict voluntary disclosures.

For example, a Certificate does not prevent researchers 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 researchers intend to make such disclosures, this should be clearly stated in the informed consent 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.

17.1.4 Application Procedures

Any person engaged in research collecting sensitive information from human research subjects may apply for a Certificate of Confidentiality. For most research, Certificates are obtained from NIH. If NIH funds the research project, the investigator may apply through the funding Institute. However, even if the research is not supported with NIH funding, the investigator may apply for a Certificate through the NIH Institute or Center (IC) funding research in a scientific area similar to the project.

If the research is conducting a sensitive research project that is covered by the AHRQ confidentiality statute (42 U.S.C. section 299a-1(c) entitled "limitation on use of certain information") or the Department of Justice confidentiality statute (42 USC section 3789g), then a CoC is not required.

If there is an Investigational New Drug Application (IND) or an Investigational Drug 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>).

17.2 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, West Virginia law mandates that certain persons who suspect child or elder abuse or neglect report this to the West Virginia Department of Health and Human Resources.

WVU policy requires the solicitation of informed consent from all adult research subjects and assent from children involved as research subjects, in addition to the consent 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.

Anyone may report suspected child abuse or neglect. Under West Virginia Law (WV Code 49-6A-2) certain persons are required to report.

Investigators should consult these sources to determine if potential subjects should be advised of mandatory reporting requirements during the informed consent process.

17.3 WVU Students and Employees as Subjects

When WVU students and/or employees are being recruited as potential subjects, researchers 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. Researchers must emphasize to subjects that neither their academic status or grades, or their employment, will be affected by their participation decision.

To minimize coercion, investigators should avoid, whenever possible, the use of their students and employees in procedures which are neither therapeutic nor diagnostic. In these latter situations, investigators should solicit subjects through means such as bulletin board notices, flyers, advertisements in newspapers, and announcements in classes or laboratories **other than their own**. When entering a classroom to recruit students and conduct research, e.g. administer a survey, investigators should 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.

17.3.1 Students in General

The fact that a person is a student can affect that person's ability to make a voluntary and uncoerced decision about participating as a subject of research.

If prospective subjects are students at WVU or any institution associated with the study, the consent form must state that class standing or grades or status on an athletic team will not be affected by refusal to participate or by withdrawal from the study.

If students are to receive class credit, other opportunities must be available to earn equivalent credit, and the consent form must so indicate.

17.3.2 Students or Trainees of an Investigator

Except in special circumstances, the Board will approve a protocol involving the investigator's current students or trainees as subjects only if the study is designed to assure anonymity, including whether or not any particular individual elected to participate. (One method of assuring anonymity is for all contact with subjects to be made by persons other than the investigator.)

17.4 Students as Researchers

The purpose of this policy is to describe requirements for research conducted by students.

17.4.1 Human Subjects Research and Course Projects

It is the policy of the IRB that research conducted by students will adhere to the regulations set forth in 45 CFR §46 as well as the ethical standards contained in the Belmont Report.

17.4.1.1 Introduction

Student participation in the research process is a valuable learning experience. The IRB supports this academic endeavor and has developed a specific policy to guide students and their advisor(s).

Students may not serve as Principal Investigators. They must have a faculty sponsor who fulfills the principal investigator eligibility criteria and who will serve as Principal Investigator and faculty advisor on the study.

17.4.1.2 Research and Clinical Practica

Research and clinical practica (usually in the form of course-related research or evaluation projects and/or directed studies) are designed to provide students an opportunity to practice various research methods such as interview, observation and survey techniques, measurement of behavior (e.g., reaction time, speech, problem solving) as well as data analysis. Typically such projects are quite limited in scope, are not considered systematic investigations designed to develop or contribute to generalizable knowledge, and are not undertaken with that goal in mind. For example, a student may interview a peer when the interview does not involve any sensitive, personal information. Such projects should not put the participants at more than minimal risk, and the data must be recorded anonymously by the students (e.g., with no names, social security numbers, or any other codes that can be linked to a list of names). These projects are considered "classroom exercises", are not systematic investigations designed to develop or contribute to generalizable knowledge, and are not subject to review by the IRB. They do not require review unless the student researcher is conducting research involving human participants (that is, the activity is a systematic investigation designed to develop or contribute to generalizable knowledge) and the student is interacting or intervening with living individuals to obtain information about those individuals or collecting private identifiable information about living individuals. If the student anticipates publishing the results or presenting at a professional meeting, consultation with the IRB should be obtained prior to beginning the activity.

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.

Students and advisors should contact the ORIC with any questions.

17.4.1.3 Research Projects (Directed or Independent)

Any research conducted by students, graduate or undergraduate that does not fall under the definition of a research or clinical practicum, which uses human beings as participants and, which is a systematic investigation designed to develop or contribute to generalizable knowledge, must be reviewed and approved by the IRB. This includes, but is not limited to, all independent undergraduate research projects and honors theses, masters' theses and dissertations that involve research involving human participants.

Recognizing the time constraints imposed on projects that must begin and be completed within a single semester, the IRB will make every effort to work with instructors to process proposals promptly. However, instructors must plan for and allow adequate time for the review process (approximately a week to a month, depending on the particular human participant issues raised by the proposed research). The later in the term a proposal is received, the more difficult it will be to accomplish the review in time for the projects to be completed during the current semester. It is very strongly urged that instructors submit proposals within the first three weeks of the semester for projects that must be completed during the current semester. In some cases, when students in a course are all using similar methods of recruitment and data collection, instructors may submit an aggregate proposal. Student research projects may be submitted to the IRB for consideration as *exempt* research if they meet federal exemption criteria such as research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior in which data is collected anonymously (e.g., with no names, social security numbers, or any other codes that can be linked to a list of names) or otherwise qualifying under exemption category 2 of the federal regulations. The course instructor must submit exemption requests to the IRB.

All *non-exempt* student research projects must be submitted for regular IRB review. Projects requiring *expedited review* are reviewed when they are submitted. Projects requiring full review by the IRB need to be submitted by one week prior to the meeting date (a list of the meeting dates and deadlines can be found at http://oric.research.wvu.edu/human_subjects_research_and_the_irb/ir).

17.4.1.4 Responsibilities of Student Advisors for all Student Research Projects

Faculty advisors as well as student researchers must have completed CITI training to conduct research with human participants, even if they are not currently conducting research with human participants.

It is the responsibility of faculty advisors to determine when an undergraduate or graduate student project does not meet the definition of a practicum and must be reviewed by the IRB. However, the advisor must have completed CITI training as noted above to be authorized to make this decision.

It is the responsibility of faculty advisors to ensure that research practica and *exempt* research activities are conducted according to the ethical standards of the relevant discipline.

When student research activities are not practica, it is the responsibility of faculty advisors to assist students in preparing review materials for the IRB and to ensure that the research is conducted in accordance with WVU's assurance with the federal government and with applicable WVU policy.

17.4.1.5 Potential Practicum Problems

Students engaged in the process of learning research techniques understandably want to focus on compelling or real-life issues. In the process of reviewing student research, however, the IRB has found topics and subjects that raise concerns for the well-being of the participants and students themselves. Projects collecting data about illegal activities, those which could cause emotional distress in the participants, those which would place the students at risk if confidentiality were breached, and those with children as participants need to be constructed with special care.

While practica are not under the purview of the IRB, the staff of the IRB is available for consultation with students and for class presentations regarding issues of the protection of the rights and welfare of human participants.

It is important to note that data collected as practica cannot at a later date normally be used for presentation at conferences, publications, or doctoral dissertations.

17.4.1.6 Activities Requiring IRB Review

"The IRB has the authority to approve, require modifications (in order to approve), or disapprove all research activities involving humans." (see [Policy #1.002](#)). This directive includes research conducted by students.

To determine if the activity meets the definition of research, the investigation must "be a systematic investigation designed to develop or contribute to generalizable knowledge". If the results of the investigation will be, or has the potential to be, published or presented through oral presentations, abstracts, or posters *outside* of the campus of

WVU, the definition of research might be indicated. Accordingly the research, if it involves human participants, is subject to IRB review.

However, if the results of the investigation will be limited to, publications, oral presentations, posters, or abstracts solely on the WVU campus, and relatedly are not systematic investigations designed to develop or contribute to generalizable knowledge, IRB review might not be required.

WVU students enrolled in graduate programs are required to have IRB approval for thesis or dissertation research projects involving human participants. **IRB review cannot occur after a study has begun.**

17.4.1.7 IRB Application and Review

There is not a special IRB review process for student research. The student researcher is expected to follow all current IRB policies and procedures for IRB initial approval, continuing review, change requests, and other protocol matters. All deadlines and time frames will remain the same as for other researchers falling under the jurisdiction of the IRB.

Key personnel for research conducted by students may include:

- a. *The student as Co-Investigator (Co-I).* It is the student's responsibility to carry out research in compliance with IRB policies and under the direction of the faculty Principal Investigator (PI).
- b. *The student's advisor as Principal Investigator(PI).* It is the responsibility of the advisor to supervise the student's research project and provide necessary advice concerning IRB requirements and applicable federal regulations. Faculty who assign or supervise research conducted by students or staff have an obligation to consider carefully whether those individuals are qualified to safeguard adequately the rights and welfare of participants and have been properly trained in human research protection.
- c. *Other applicable Supervising Investigators and/or participating personnel.*

17.4.1.8 Training in the Protections of Human Participant Requirements

The IRB requires that all key study personnel involved in the conduct of human participant research be certified by completion of the web-based training program (CITI). All students conducting research requiring IRB review must complete CITI training prior to IRB approval of the research. This includes *exempt* research.

Students participating in classroom projects that *do not* require IRB review are *not* required to complete CITI training. However, some colleges, departments, and sections may adopt internal requirements for all students to complete CITI training.

17.5 Oral History

The following is based on guidance received from OHRP:

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 HHS 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 HHS 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 which 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 Organization's 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 3.1 above.

General principles for evaluating Oral History type 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 would NOT constitute "research" as defined by HHS regulations 45 CFR part 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 HHS regulations at 45 CFR part 46.

Example: An open ended interview of surviving Gulf War veterans to document their experiences and to draw conclusions about their experiences, inform policy, or generalize findings.

3. Oral historians and qualitative investigators may want to create archives for the purpose of providing a resource for others to do research. Since the intent of the archive is to create a repository of information for other investigators to conduct research as defined by 45 CFR part 46, the creation of such an archive WOULD constitute research under 45 CFR part 46.

Example: Open ended interviews are conducted with surviving Negro League Baseball players in order to create an archive for future research. The creation of such an archive would constitute research under 45 CFR part 46 since the intent is to collect data for future research.

Investigators are advised to consult with the ORIC regarding whether their oral history project requires IRB review.

17.6 Genetic Studies

Genetic research studies may create special risks to human subjects and their relatives. These involve medical, psychosocial, 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?

17.7 Research Involving Coded Private Information or Biological Specimens

WVU policy is based on the OHRP guidance document entitled, “**Guidance on Research Involving Coded Private Information or Biological Specimens**” (August 10, 2004 <http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>). This document:

1. Provides guidance as to when research involving coded private information or specimens is or is not research involving human subjects, as defined under HHS regulations for the protection of human research subjects (45 CFR part 46).
2. Reaffirms OHRP policy that, under certain limited conditions, research involving **only** coded private information or specimens is not human subjects research.
3. Provides guidance on who should determine whether human subjects are involved in research.

For purposes of this policy, *coded* means that: (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

Under the definition of human subject in Section 2 of this policy, *obtaining* identifiable private information or identifiable specimens for research purposes constitutes human subjects research. *Obtaining* means receiving or accessing identifiable private information or identifiable specimens for research purposes. This includes an investigator’s use, study, or analysis for research purposes of identifiable private information or identifiable specimens already in the possession of the investigator.

In general, private information or specimens are considered to be individually identifiable when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. Private information or specimens are not considered to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Research involving **only** coded private information or specimens do **not** involve human subjects if the following conditions are both met:

- the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals;

and

- the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
 - a. the key to decipher the code is destroyed before the research begins;
 - b. the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any

circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement); data use agreement

- c. there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
- d. there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

In some cases an investigator who obtains coded private information or specimens about living individuals under one of the conditions cited in 2(a)-(d) above may (1) unexpectedly learn the identity of one or more living individuals, or (2) for previously unforeseen reasons now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained private information or specimens pertain, then the research activity now would involve human subjects. Unless this human subjects research is determined to be exempt (See Section 3.3), IRB review of the research would be required. Informed consent of the subjects also would be required unless the IRB approved a waiver of informed consent (See Section 5.8).

17.7.1 Who Should Determine Whether Coded Private Information or Specimens Constitutes Human Subjects Research

The investigator in consultation with the IRB Chair or Director of the ORIC will determine if the research involving coded information or specimens requires IRB review. If the request is verbal (by phone or in person) or by email, it is the investigator's responsibility to maintain documentation of such a decision. If the investigator submits a formal submission, the request must include sufficient documentation of the activity to support the determination. Formal submissions will be responded to in writing and a copy of the submitted materials and determination letter/email will be kept on file.

17.8 Case Reports Requiring IRB Review

In general, an anecdotal report on a series of patients seen in one's own practice and a comparison of these patients to existing reports in the literature is not research and would 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 would be considered research and would require IRB approval.

17.8.1 Definitions

Single Case Report: The external reporting (e.g., publication or poster/verbal 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 or poster/verbal presentation) of an interesting clinical situation or medical condition in a series of patients (i.e., more than one patient). Case series usually contain detailed information about each patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.

17.9 International Research

The IRB will review all international research utilizing 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.

The WVU IRB must receive and review the foreign institution or site’s IRB review and approval of each study prior to the commencement of the research at the foreign institution or site.

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 are permitting the research to be conducted at the performance site.
- IRB approval to conduct research at the foreign institution or site is contingent upon receiving documentation of the performance site’s IRB/IEC determination, or letter of cooperation, as applicable.
- It is the responsibility of the WVU Investigator and the foreign institution or site to assure that the resources and facilities are appropriate for the nature of the research.

- It is the responsibility of the WVU Investigator and the foreign institution or site to confirm the qualifications of the Researchers and Research Staff for conducting research in that country(ies).
- It is the responsibility of the WVU Investigator and the foreign institution or site to ensure that the following activities will occur.
 - Initial review, continuing review, and review of modification
 - Post-approval monitoring
 - Handling of complaints, non-compliance and unanticipated problems involving risk to subjects or others.

The IRB will not rely on a local ethics committee that does not have policies and procedures for the activities listed above.

- It is the responsibility of the WVU 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 consenting research participants, etc.).
- The IRB will consider local research context when reviewing international studies to assure protections are in place that are appropriate to the setting in which the research will be conducted, including knowledge of local laws and cultural context.
- In the case where there is no local IRB review the IRB may require an expert consultant, either from the local country where the research is conducted or from an international organization, with the expertise or knowledge required to adequately evaluate the research in light of local context.
- The informed consent documents must be in a language understandable to the proposed participants. Therefore, the IRB will review the document and a back translation of the exact content contained in the foreign language informed consent document which must be provided by the Investigator, with the credentials of the translator detailed in the IRB application or amendment form. Verification of the back translation should be made available for the IRB file.

17.9.1 Monitoring of Approved International Research

The IRB is responsible for the ongoing review of international research conducted under its jurisdiction through the continuing review process in accordance with all applicable federal regulations.

When the IRB and a local ethics committee will both be involved in the review of research, there is a plan for coordination and communication with the local ECs.

The IRB will require documentation of regular correspondence between the WVU Investigator and the foreign institution or site and may require verification from sources other than the WVU Investigator that there have been no substantial changes in the research since its last review.

17.10 Community Based Research (CBR)

Community based research 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, 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, PIs 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. ORIC will assist the PI in developing such arrangements.

The following are some questions that PIs should ask as they develop CBR. These are also the questions that the IRB should consider when reviewing CBR.

17.10.1 CBR Questions

Background, purpose, objectives

How was the community involved or consulted in defining the need?

Who came up with the research objectives and how?

Is this research really justified with respect to community concerns?

Are there concrete action outcomes?

Who benefits? How?

Research methodology

How will the community be involved in the research? At what levels?

What training or capacity-building opportunities will be built in?

Procedures

Will the methods used be sensitive and appropriate to various communities (consider literacy issues, language barriers, cultural sensitivities, etc.)?

How will scientific rigor and accessibility be balanced?

Participants

Are the appropriate people being included to get the questions answered (e.g., service providers, community members, leaders etc.)?

How will the research team protect vulnerable groups?

Will the research process include or engage marginalized or disenfranchised community members? How?

Is there a reason to exclude some people? Why?

Recruitment

What provisions have been put in place to ensure culturally-relevant and appropriate recruitment strategies and materials?

Have “power” relationships been considered in the recruitment strategies to minimize coercion?

Who approaches people about the study and how?

Risks and benefits

What are the risks and benefits of the research for communities? For individuals?
Are the risks (including risks to the community) being presented honestly?
How will risks be minimized?

Privacy and confidentiality

Where will data be stored? Who will have access to the data? How?
What processes will be put in place to be inclusive about data analysis and yet maintain privacy of participants?
What will be the rules for working with transcripts or surveys with identifying information?
How will boundaries between multiple roles (e.g., researcher, counselor, peer) be maintained?

Compensation

How will people be reimbursed for their time and honor their efforts without it becoming coercive.
How will compensation be approached?
What provisions have been made for minimizing barriers to participation (e.g., providing for food, travel, childcare)?
Who is managing the budget? How are these decisions negotiated?

Conflicts of interest

What happens when the PI/research staff is the friend, peer, service provider, doctor, nurse, social worker, educator, funder, etc.
How will power differentials be appropriately acknowledged and negotiated?

Informed consent process

What does informed consent mean for “vulnerable” □ populations (e.g., children, mentally ill, developmentally challenged)?
What processes are in place for gathering individual consent?
Where written informed consent is not being obtained, explain why.
What processes are in place for gathering community consent?
Where minors are to be included as participants, how will assent be obtained?
Are the consent processes culturally sensitive and appropriate for the populations being included?

Outcomes and results

How will the research be disseminated to academic audiences?
How will the research be disseminated to community audiences?
What are the new ways that this research will be acted upon to ensure community/policy/social change?

Ongoing reflection and partnership development

Is there a partnership agreement or memorandum of understanding to be signed by all partners that describes how they will work together?

What internal process evaluation mechanisms are in place?

When plans change to accommodate community concerns (as they invariably do in CBR), how will this be communicate to the IRB?

Based on:

Ethical Dilemmas in Community-Based Participatory Research: Recommendations for Institutional Review Boards

Sarah Flicker, Robb Travers, Adrian Guta, Sean McDonald, and Aileen Meagher

J Urban Health. 2007 July; 84(4): 478–493.

Published online 2007 April 10. doi: 10.1007/s11524-007-9165-7.

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17.11 Studies Involving Suicide Ideation

If your protocol:

- Has a research purpose to study suicide, suicidal ideation, depression or trauma;
- Has a research purpose to study traumatic life events that may evoke powerful emotion or induce changes of mood in participants;
- Includes assessments (e.g., surveys, exams, questionnaires, etc.) that can be used to identify suicidal ideation (thoughts of suicide, either active or passive), plan (the means or mechanism) or intent (the expressed desire and willingness to act on the plan);

Then your protocol:

- Should include research staff who are qualified to assess suicidality, when possible;
- Must describe a plan to link participants with psychological help if needed, and include written materials listing those resources as an attachment to the protocol;
- Must describe a plan to address the situation if a participant is assessed to be a danger to themselves, but refuse treatment.

PLANS might say (for example):

- If a protocol uses WVU students as participants, plan might describe providing contact information for or an escort provided to the Carruth Center/WellWVU.
- If a protocol is in the local community, the PI might provide a list of local psychiatry/psychotherapy providers.

- If a participant is assessed to be actively suicidal, but refuses assistance, the plan might include steps to contact the Mental Hygiene Commissioner and/or call 911.