

MARSHALL UNIVERSITY



OFFICE OF
RESEARCH INTEGRITY

**Standard Operating Procedures
For The
Human Research Protection Program
(HRPP)**

Prologue

This Guide is based on applicable federal regulations, West Virginia state statutes, and Marshall University Policy as they pertain to the conduct of human subject research at Marshall University.

This Standard Operating Procedures (SOP) is intended to be a dynamic and useful document. We welcome your comments about the contents and structure. If you have suggestions on how to improve the document, please send your suggestions to the Office of Research Integrity using the comments section or email us your comments.

Policy

It is the policy of Marshall University that human research activities conducted under the oversight of the organization will be conducted in accordance with applicable federal law and regulations that include but are not limited to Federal Regulations 45 CFR 46, 21 CFR 50, 21 CFR 56, 38 CFR 16, and 45 CFR 160, 162, and 164, applicable West Virginia state statutes and regulations, the principles of the Belmont Report and local University Institutional Review Board (IRB) requirements.

The Office of Research Integrity (ORI) supports the institution in promoting ethical conduct of research and ensures the University's solid commitment to the compliance with all applicable regulations and accreditation standards. Marshall has an established Federal Wide Assurance (FWA #00002704) with the Office of Human Research Protections (OHRP).

The office currently provides support for both a Medical (IRB#1) and a Behavioral and Social Sciences (IRB#2) Institutional Review Board, the Institutional Animal Care and Use Committee (IACUC), Conflict of Interest in Research Committee, and addresses the issues concerning Biohazards in research. ORI also supports the institution in promoting ethical conduct of research and educating Marshall students and employees regarding research misconduct regulations.

Marshall University does not apply the International Conference on Harmonization/Good Clinical Practice (ICH-GCP) requirements to all human subject research. As such, it is the PI's responsibility to request that the IRB apply ICH-GCP requirements to their individual study. GCP standards contained in the ICH document are not regulatory requirements in the United States and vary from FDA and DHHS regulations. Although the MU IRB#1 and SOP do not voluntarily apply the ICH-GCP requirements to all human subject research, they are in accordance with ICH-GCP guidelines regarding Institutional Review Board/Independent Ethics Committee (IRB/IEC) criteria 3.1 through 3.4 of E-6 for all human subject research. Researchers can apply to have their individual study comply with all the ICH-GCP requirements.

No Marshall University faculty or staff member is permitted to be part of a research team conducting human subject research at Marshall University that has not received an IRB approval.

Mission Statement

The mission of the Marshall University Human Research Protection Program is to protect the rights, welfare and privacy of human subjects who choose to participate in human subject research. The program is committed to advancing responsible conduct in research, ethical treatment of human research subjects, and ensuring that the right of every human being to voluntary, informed consent to research is respected. To achieve this goal, each University Institutional Review Board (IRB) will:

- 1) Require each IRB member, principal investigator, staff member and student involved in research to complete education in human subject research.
- 2) Review all research involving human subjects prior to study initiation.
- 3) Adhere to the principles of the Belmont Report and the established criteria set forth by the Department of Health and Human Services.

The Office of Research Integrity (ORI) will serve this mission by:

- 1) Providing administrative support to all the University's IRB's.
- 2) Providing and maintaining an educational program designed to educate everyone involved in human research in the safe and ethical conduct of research that will protect human subjects.

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Chapter 1 - Introduction

Definition of Human Subject Research:

Activities are human subject research under DHHS regulations when they meet the DHHS definition of “**research**” (45 CFR §46.102(l)) and involve a “**human subject**” as defined in DHHS regulations (45 CFR §46.102(e)).

Activities are human subject research under FDA regulations when they meet the FDA definition of “**research**” (21 CFR §50.3(c), 21 CFR §56.103(c), 21 CFR §312.3(b), or 21 CFR §812.3(h)) and involve a “**subject**” as defined in FDA regulations (21 CFR §50.3(g), 21 CFR §56.103(e), 21 CFR §312.3(b), or 21 CFR §812.3(p))

Research:

Under DHHS regulations (45 CFR §46.102(l)) is defined as: *A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.*

Under FDA regulations (21 CFR §50.3(c)) is defined as: *Any experiment that involves a test article and one or more human subjects, and that either is subject to requirements for prior submission to the Food and Drug Administration.*

Human Subject:

Under DHHS Regulations (45 CFR §46.102(e)) is defined as: *A living individual about whom an investigator (whether professional or student) conducting research:*

- (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or*
- (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.*

Under FDA regulations (21 CFR §50.3(g)) a human subject is defined as:

- 1) An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A participant may be either a healthy human or a patient.
- 2) Or in the case of a medical device: A human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A participant may be in normal health or may have a medical condition or disease.

For Department of Defense-sponsored research the definition of “experimental subject” is:

Subject: An activity, for research purposes, where there is an intervention or interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction (32CFR219.102(f), reference (c)). Examples of interventions or interactions include, but are not limited to, a physical procedure, a drug, a manipulation of the subject or subject's environment, the withholding of an intervention that would have been undertaken if not for the research purpose.

Definition of Engaged in Research:

A person is considered engaged in a particular non-exempt human subjects research project when he/she for the purposes of the research project obtain: (1) data or biospecimens related to the subjects of the research through intervention or interaction with them; (2) identifiable private information or identifiable biospecimens related to the subjects of the research; or (3) the informed consent of human subjects for the research.

What is Not Human Subject Research:

Data collection for internal departmental, school, or other institutional administrative purposes. (i.e. teaching evaluations, customer service surveys)

Information-gathering interviews where questions focus on things, products, or policies rather than about people or their thoughts. (i.e. canvassing librarians about inter-library loan policies or rising journal costs)

Publicly available data does not require IRB approval. (i.e. for internal departmental, school, or other institutional administrative purposes. (i.e. teaching evaluations, customer service surveys)

Coded data that were not collected for the currently proposed projects as long as the investigator receiving the data cannot link the data back to the individual.

Case Studies which are published and/or presented at national or regional meetings are often **not** considered human subject research if the case is limited to a description of the clinical features and/or outcome of a single patient and do not contribute to generalizable knowledge. (for example: the comparison of case studies would qualify as human subject research)

Note: When there is any doubt as to whether or not a study could qualify as human subject research, you should submit an abstract to ORI for an IRB Chair to review and make a determination.

When following Department of Justice regulations:

- For research conducted within the Bureau of Prisons: Implementation of Bureau programmatic or operational initiatives made through pilot projects is not considered to be research.

When following DHHS requirements:

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

The following activities are not considered research:

- Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.
- Public health surveillance activities conducted by a public health authority, limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance.
 - Including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority.
 - Including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products.
 - Including those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).
- Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
- Authorized operational activities (as determined by the relevant federal agency) in support of intelligence, homeland security, defense, or other national security missions.
- Secondary research involving non-identifiable newborn screening blood spots.

When following FDA regulations:

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

Chapter 2 - Administration (IRB)

PURPOSE: To establish the guidelines for administrative support of the Marshall University Human Research Protection Program (HRPP) and Institutional Review Board (IRB).

POLICY: In accordance with 38 CFR 16.103(b)(2) and the Common Rule, this facility provides the Office of Research Integrity (ORI) and the Institutional Review Board (IRB) with sufficient meeting space, equipment, and staff to support the HRPP's and IRB's review and record keeping responsibilities.

RESPONSIBILITIES:

Institutional Official - As the Assurance Signatory Official (Institutional Official), the Vice President for Research is responsible for ensuring the IRB has sufficient administrative and clerical support to assist the IRB in fulfilling obligations as well as allocating space, and equipment. The Vice President for Research is also responsible to annually (or more frequently) evaluate whether the number of IRB's is appropriate to the volume and types of human research reviewed, so that reviews are accomplished in a thorough and timely manner. The Vice President for Research is also responsible to adjust the number of IRBs as needed and to annually review and adjust the membership and composition of the IRB to meet regulatory and organizational requirements.

Director, Office of Research Integrity - The Director, ORI is responsible for (1) directing and overseeing all HRPP and IRB support functions and operations; (2) training, supervising, and evaluating IRB staff; (3) developing and implementing procedures to effect efficient document flow and maintenance of all IRB records; and (4) Coordination and communication with local IRBs when appropriate.

If Marshall University relies upon the services or components of another organization the Director, ORI is responsible to evaluate whether the service or component is AAHRPP accredited or meets the relevant standards. The MOU or agreement must describe how responsibilities are divided between Marshall University and the vendor.

IRB Chairperson – The IRB Chairperson is responsible for keeping the Director, ORI and the Institutional Official abreast of administrative and resource needs and make requests based on the assessed needs of his/her IRB.

IRB Coordinator - The IRB Coordinator is responsible for maintaining the official roster of IRB members, scheduling meetings, distributing pre-meeting materials, compiling the minutes of IRB meetings in compliance with regulatory requirements, maintaining all IRB documentation and records in accordance with regulatory requirements in IRBNet software and provides additional support to the IRB as required.

In addition, the IRB Coordinator has the following responsibilities:

- 1) When research is to be conducted in a foreign country(ies), ensuring appropriate expertise and knowledge of the country(ies) either through an IRB member or consultants.
- 2) Confirming the qualifications of the researchers and research staff for conducting research in that country.
- 3) To work with the investigator to obtain the proper documentation for research in a foreign country.
- 4) Ensuring documentation of permission to conduct research from local authority or ethic committee in that country. If these authorities do not apply then documentation should be provided to support that situation and describe the customs of that community within the foreign country.
- 5) Ensuring all submissions are complete and accurate, including initial review, continuing review, and review of modifications to previously approved research.
- 6) Post-approval monitoring.
- 7) Handling of complaints, non-compliance, and unanticipated problems involving risk to participants or others.

Principal Investigator - The principal investigator has the ultimate responsibility for ensuring the proper conduct of the study. The principal investigator must ensure that his research staff is also knowledgeable of issues related to the study. In addition to those duties the principal investigator is also responsible for:

- 1) Ensuring knowledge of local laws.
- 2) Ensuring knowledge of cultural context.
- 3) Conduct of the consent process, documentation and all other language issues.
- 4) Provide documentation of permission to conduct research from local authority or ethic committee in that country. If these authorities do not apply then documentation should be provided to support that situation and describe the customs of that community within the foreign country.

Resources Allocation. Personnel, space, and equipment are allocated based on the needs of the IRB.

Research Management Specialist (IRB#2 Coord)	1.0 FTEE
IRB#1 Coordinator	1.0 FTEE
Meeting Space	As needed
Computers, copier, fax, printers, and phones	As needed

Legal Counsel. The Marshall University general counsel serves as the IRB, Conflict of Interest, and any other needed legal counsel for advice. When legal assistance is needed, the Vice President for Research will evaluate the need for additional resources, including outside legal consultation, and obtain that assistance if required.

PROCEDURES:

- 1) The IRB Chairperson determines, at least annually, the assessed need for personnel, space and equipment. The resource needs are requested through the Director, ORI to the Institutional Official.
- 2) The IRB Chairperson determines the dates/times of IRB meetings that are outside the norm of every second Wednesday of the month for IRB #1, and every third Wednesday of the month for IRB #2.
- 3) The IRB Coordinator maintains the official roster of IRB members, schedules meetings, distributes pre-meeting materials at a minimum (if possible) of one week prior to the meeting, and compiles the minutes of IRB meetings in compliance with regulatory requirements. The IRB Coordinator maintains all IRB documentation and records in accordance with regulatory requirements and ensures that all IRB records are secured and properly archived. IRBNet, an online submission system, is utilized to track the progress of each research protocol submitted. The IRB Coordinator serves as a resource for investigators on general regulatory information, provides guidance about forms and submission procedures and facilitates communication between investigators and the IRB. The IRB Coordinator assists new IRB members in completing orientation procedures and meeting required education standards, trains research investigators and staff while maintaining reference materials related to human subject protection requirements. The IRB Coordinator drafts reports and correspondence to research investigators on behalf of the IRB or IRB Chairperson regarding the status of the research, including conditions for approval of research and cases of adverse events or unanticipated problems. In addition, the IRB Coordinator maintains and updates the IRB forms.

Chapter 3 - Behavioral and Social Sciences Research

PURPOSE: To define and explain Behavioral and Social Science research (also known as Social/Behavioral/Educational Research – SBER).

POLICY: To ensure that the appropriate type of review is conducted within the constraints of the federal regulations and the facility's policies and procedures.

SCOPE: This policy covers Behavioral and Social Sciences research conducted under the auspices of IRB#2. Behavioral and Social Sciences research involves surveys, observational studies, personal interviews, or experimental designs involving exposure to some type of stimulus or intervention.

RESPONSIBILITIES:

IRB Chairperson is responsible for ensuring that the appropriate type of review is conducted within all federal regulations and organization's policies and procedures.

IRB Members are responsible for ensuring the reviews are conducted appropriately, ethically, and within the constraints of the federal regulations and organizational policies.

Principal Investigator (PI) is responsible for ensuring that every research subject's rights, welfare, and safety are protected. The PI is responsible for the protocol design, which must minimize risks to subjects while maximizing benefits. The PI must ensure that all members of the research team always comply with the findings, determinations, and requirements of the IRB. The PI must also ensure the adequacy of the informed consent process, regardless of which members of the research team are authorized to actually obtain and document consent.

IRB Coordinator is responsible for maintaining the documentation of the activities of the IRB and reporting the information at the next IRB meeting.

CONCERNS OF BEHAVIORAL AND SOCIAL RESEARCH:

A. Social and Psychological Harms. The IRB carefully examines the research to determine the probability of risk or harm to subjects. These considerations apply to medical/biological research as well as social and behavioral research.

- 1) The IRB considers the potential for participants to experience stress, anxiety, guilt, or trauma that can result in genuine psychological harm.
- 2) The IRB considers the risks of criminal or civil liability or other risks that can result in serious social harms, such as damage to financial standing, employability, insurability, reputation, stigmatization, and damage to social or family relationships.

- 3) If information is being collected on living individuals other than the primary “target” subjects the IRB considers the risk of harm to those “non-target” individuals, as well.

The IRB reviews the proposal for appropriate preventive protections and debriefings, adequate disclosure of risks in the informed consent information, and mechanisms to protect the confidentiality and privacy of persons participating in or affected by the research.

B. Privacy and Confidentiality Concerns. The use of confidential information is an essential element of social and behavioral research. These considerations apply to medical/biological research as well as social and behavioral research.

- 1) The IRB ensures that the methods used to identify potential research subjects or to gather information about subjects do not invade the privacy of the individuals. In general, identifiable information may not be obtained from private (non-public) records without the approval of the IRB and the informed consent of the subject. This is the case even for activities intended to identify potential subjects who will later be approached to participate in research.
- 2) The IRB ensures that adequate measures are taken to protect individually identifiable private information once it has been collected to prevent a breach of confidentiality that could lead to a loss of privacy and potentially harm subjects.

C. Safeguarding Confidentiality. When information linked to individuals will be recorded as part of the research design, the IRB ensures that adequate precautions will be taken to safeguard the confidentiality of the information. The more sensitive the data being collected, the more important it is for the researcher and the IRB to be familiar with techniques for protecting confidentiality.

PROCEDURES:

A. Exempt Review. To obtain exempt status the research activity must meet one of the below listed categories as listed in 45CFR46.104(d):

(Note: There are several references to a **limited IRB review**. A limited IRB review is conducted by the IRB Chair/Designee (IRB member) to ensure that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. Studies that qualify under Exempt categories 2, 3, 7, & 8 may require a limited IRB review. The study is processed like an Exempt study but the review must be conducted by the IRB Chair/Designee. If an IRB member reviewing the research by limited IRB review finds that research is greater than minimal risk, the reviewer must document the rationale for this determination and the rationale for review by the convened IRB. The IRB member conducting limited IRB review may not disapprove research and Marshall University retains the authority to suspend or terminate IRB approval of research approved with a limited review.)

- 1) Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students’ opportunity to learn required educational content or the assessment of educators who provide

instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

- 2) Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:
 - i. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
 - ii. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
 - iii. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).
- 3) Research involving benign interventions:
 - i. Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:
 - (a) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
 - (b) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
 - (c) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).
 - ii. For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online

game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

- iii. If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.
- 4) Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:
- i. The identifiable private information or identifiable biospecimens are publicly available;
 - ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;
 - iii. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or
 - iv. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.
- 5) Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or

grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended. There must also be no statutory requirement that an IRB review the research and the research must not involve significant physical invasions or intrusions upon the privacy of subjects.

- i. Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal website or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

6) Taste and food quality evaluation and consumer acceptance studies:

- i. If wholesome foods without additives are consumed, or
- ii. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the 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.

7) Storage or maintenance for secondary research for which broad consent is required:

Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §46.111(a)(8).

8) Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:

- i. Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §46.116(a)(1) through (4), (a)(6), and (d);
- ii. Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §46.117;
- iii. An IRB conducts a limited IRB review and makes the determination required by §46.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (i) of this section; and

- iv. The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

B. Expedited Review. Behavioral and Social Science research qualifies for expedited review if the research:

- Presents no greater than minimal risks to subjects.
- Includes reasonable and appropriate protections so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal, if the identification of the participants or their responses will reasonably place them at risk of criminal or civil liability or be damaging to their financial standing, employability, insurability, reputation, or be stigmatizing.
- Is not classified.
- Fits one (or more) of the following expedited categories:

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

- (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
- (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR 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, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; **or**
- (b) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

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

Examples: (a) hair and nail clippings in a non-disfiguring 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 gumbase 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 non-research purposes (such as medical treatment or diagnosis).
- 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.

C. Expedited Continuing Review of Full Board Studies:

- 1) Expedited 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.

- 2) Expedited 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.

Research Involving Existing Data and Documents. Minimal risk research involving materials, (including data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes, may be reviewed using expedited procedures.

Research Involving Data from Voice, Video, Digital, or Image Recordings Made for Research Purposes. The IRB may utilize expedited procedures to review research that involves the collection of data from voice, video, digital, or image recordings made for research purposes.

Research Involving Individual or Group Characteristics or Behavior or Research Employing Survey, Interview, Oral History, Focus Group, Program Evaluation, Human Factors Evaluation, or Quality Assurance Methodologies. The IRB may utilize expedited procedures to review the following:

- 1) Research on individual or group characteristics or behavior, or
- 2) Research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.
- 3) This category covers a wide range of non-exempt social and behavioral research activities when they present no greater than minimal risk to subjects. Examples include, but are not limited to, research on perception, cognition, motivation, identification, language, communication, cultural beliefs or practices.

Research Involving Deception or Withholding of Information. The IRB applies both common sense and sensitivity to the review of research involving incomplete disclosure or outright deception. Where deception is involved, the IRB needs to be satisfied that the deception is necessary and that, when appropriate, the subjects shall be debriefed. (Debriefing may be inappropriate, for example, when the debriefing itself would present an unreasonable risk of harm without a corresponding benefit.) The IRB has the responsibility for assuring that the proposed subject population is suitable.

Deception can only be permitted where the IRB documents that a waiver of the usual informed consent requirements is justified under the following criteria and the IRB must find and document that all four of the following criteria have been satisfied:

- 1) The research presents no more than minimal risk to subjects;
- 2) The research could not practicably be carried out without the waiver or alteration;

- 3) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
- 4) The waiver or alteration shall not adversely affect the rights and welfare of the subjects; and
- 5) Where appropriate, the subjects shall be provided with additional pertinent information after participation.

In making the determination to approve the use of deception under a waiver of informed consent, the IRB considers each criterion in turn, and documents specifically, in the IRB minutes and/or in the IRB protocol file, how the proposed research satisfies that criterion.

Department of Justice Regulations. For research conducted within the Bureau of Prisons, the organization, IRB, and researchers and research staff must follow the requirements of 28 CFR 512, including:

- 1) The project must not involve medical experimentation, cosmetic research, or pharmaceutical testing.
- 2) The research design must be compatible with both the operation of prison facilities and protection of human subjects. The researcher must observe the rules of the institution or office in which the research is conducted.
- 3) Any researcher who is a non-employee of the Bureau must sign a statement in which the researcher agrees to adhere to the provisions of 28 CFR 512.
- 4) All research proposals will be reviewed by the Bureau Research Review Board.

Chapter 4 - Budget

PURPOSE: To delineate the funding and expenditure procedures as established by Marshall University guidelines.

POLICY: The Human Research Protection Program's budget policy is to secure, appropriate, and disburse funding according to the Marshall University guidelines.

SCOPE: This policy covers all budgetary areas in the Office of Research Integrity and all research activities.

RESPONSIBILITIES:

Vice President for Research is responsible for accomplishing the research mission at the institution and following all state and federal fiscal management policies and procedures.

Director of the Office of Research Integrity (ORI) is responsible for the budgetary functions of the Human Research Protection Program. The Director is responsible for identifying and reporting budgetary needs, appropriations, disbursements, and discrepancies to the Vice President for Research.

Marshall University Research Corporation (MURC) is responsible for maintaining the daily budget, receiving funds, disbursing funds and invoicing for any applicable study fees.

PROCEDURES:

A. Funding Mechanisms

- 1) **Intramural Funds.** State appropriated funds are allocated to support the Office of Research Integrity (ORI) at Marshall University as well as those provided through the auspices of the Marshall University Research Corporation (MURC).
- 2) **Extramural Funds.** Extramural funds are funds other than those specifically appropriated by state appropriations that are made available at any time to support the activities of ORI. These funds may be provided by other Federal agencies, local government agencies, non-profit corporations or foundations, other charitable organizations, corporations, or an individual contributor. Such funds include:
 - (a) Gifts or donations received for research projects with the approval of the Director. These include donations of equipment or supplies, as well as funding by non-profit foundations, private donors, and corporations.
 - (b) Grants or contracts that have been approved by the Director.

- (c) Reimbursables are extramural funds provided in support of a Memorandum of Understanding (MOU) with another institution whereby ORI provides specific services (e.g., IRB reviews) or a grant from a non-VA government organization.
- 3) Cooperative Research and Development Agreements (CRADA).
- 4) Fees from Industry sponsored research studies.

B. Distribution and Expenditure of Funds

- 1) **Funds Provided to the Office of Research Integrity.** Prior to the beginning of each fiscal year, the Vice President of Research, in concert and collaboration with the Director of ORI, assigns an initial operating level of monetary allocations for the projected operations of ORI. The Vice President for Research may approve additional funds for ORI activities as deemed necessary throughout the fiscal year. Other extramural funds may be received locally during a fiscal year.
- 2) **Institutional Responsibilities and Administrative Support.** Cost centers are used to ensure that costs are charged to the correct ORI program. A common resource is a facility, function, or piece of equipment shared commonly by several programs.
 - (a) Administration of Funds. The following entities may administer funds for ORI-approved activities, in accordance with applicable state law and Marshall University:
 - i. Marshall University administers all intramural funds, all funds in the Departmental Operating Budget Fund earmarked for ORI administration, and all funds received from another state or Federal agency under an interagency agreement.
 - ii. The Marshall University Research Corporation, MURC, administers all funds that the corporation receives.
 - (b) Administration of Contracts. Contracts may be awarded for ORI purposes. Some examples of activities to be achieved by contract include but are not limited to: written consultative opinions, reviews, and critiques of research proposals or ongoing projects; and statistical analyses and tabulations. The ORI shall award contracts for research purposes only when the ORI cannot provide the service and in order to accomplish its specific goals and objectives.
 - i. Contracts must be in compliance with state acquisition regulations.
 - ii. All contract negotiations are to be handled by the contracting officer. Only a contracting officer is empowered by state law to execute the contract. There must be technical or scientific assistance, however, from the principal investigator or from a contracting officer's technical representative designated by the ORI. No contract will be written for a period exceeding 1 year (although

option years may be included), and each will specifically contain the information outlined in University policy.

- (1) Commercially available supplies, devices, and services can be obtained within the allowed dollar limits by local contract for use in an approved project.
 - (2) In the case of consultant services, Letters of Agreement may be used subject to institutional policies and controls as outlined in current MU regulations. Any questions about applicability should be directed to the contracting officer.
- (c) Administration of Inter-institutional Agreements. The Office of Research Integrity may enter into inter-institutional agreements with other institutions to provide a portion(s) of their overall Human Research Protections Program such as IRB reviews. Such agreements provide a means by which Marshall University may provide service or product contracts with another institution or department, which has a need for the required services. The funding for an inter-institutional agreement is provided through a reimbursable mechanism. The reimbursement to ORI for the service provided is accomplished by billing the other institution's appropriated fund and then issuing the funds to ORI.

Departmental Operating Budget Fund Procedures. Departmental Operating Budget Funds will be managed according to current MU financial management policies and procedures.

Policies and Procedures. As set forth in Funds:

- 1) The Director of ORI may authorize expenditures from the balances of the institution's earmarked Departmental Operating Budget Funds for the purpose(s) for which the funds have been designated.
- 2) All withdrawals from the Departmental Operating Budget Funds must be approved by the Director or his designee and recorded as obligations prior to release of purchase documents or expenditures. The approval may be indicated on the purchase document.
- 3) Expenditures from the Departmental Operating Budget Fund for ORI activities are limited to funds specifically earmarked by the donor for such purpose(s).
- 4) The Director may authorize travel from earmarked Departmental Operating Budget monies, which support an approved HRPP activity, provided the travel is essential to the conduct of the ORI. Travel will be authorized and performed in accordance with existing state directives and travel regulations.
- 5) The costs associated with the IRB-related activities of the ORI shall be shared equitably between each IRB-related institution.

Charging Industry Sponsors for IRB Review. The revenue collected for charging for the IRB services can be utilized to defray administrative direct and indirect costs and to obtain other necessary resources and external services. A fee for IRB review for supported protocols will provide improved services. Payment cannot be dependent upon approval of the study.

Monetary Fees for IRB Reviews. The IRB review charge will appear as a separate category distinct from the project budget within the contract. The principal investigator assumes responsibility for ensuring that fees are paid. Checks should be made to the Marshall University Research Corporation and must include the IRB protocol number.

Fees: If the full convened or expedited protocol is industry sponsored, the ORI will be charging the sponsor a one time fee of \$2,500 that will cover the initial review and all continuing IRB reviews. The fee is the same for industry sponsored expedited reviews. Payment is to be made to the Marshall University Research Corporation and must accompany the study application. With approval of the Director ORI, a verification of allocated funds can accompany the application in lieu of payment.

Waivers: There may be extenuating circumstances where such a charge would be unwarranted (e.g., small project budgets). Please send written requests for waiver of the IRB fee to the Director, ORI, Applied Engineering Complex, Room 4211, One John Marshall Drive, Huntington, WV 25755.

Chapter 5 – Central/External IRB Review

PURPOSE: To establish guidelines with regard to the acceptance of Central IRB (CIRB) protocols in accordance with DHHS regulations at 45CFR46.114. A list of currently approved CIRBs can be obtained from the Office of Research Integrity.

POLICY: To establish a system designating the IRB#1 Coordinator as the person responsible to conduct the administrative review of CIRB studies submitted under a total reliance model.

DEFINITIONS:

Central Institutional Review Board (CIRB). CIRBs are designed to help reduce the administrative burden on local IRBs and investigators when they participate in multi-center trials. Marshall University's Office of Research Integrity (ORI) use of the CIRB total reliance (or independent) model enables an investigator to enroll subjects into sponsored studies or adult, Cooperative Group, clinical trials in a more expeditious manner.

RESPONSIBILITIES:

The following division of responsibilities is based on the contracts reflecting that the CIRB/External IRB is the sole IRB of record responsible for both study review as well as review of local context considerations for Marshall University. In a total reliance model (i.e. NCI CIRB) the CIRB/External IRB requires information describing local context considerations. The local context considerations are identified and reported to the CIRB/External IRB by various means as established by each CIRB/External IRB. Local context considerations include, but are not limited to, resources available to support research, extent of existing research responsibilities, informed consent process information, including descriptions of vulnerable populations eligible for enrollment and safeguards used to protect those populations. Privacy and confidentiality protections, in addition to any unique study-specific considerations, are also reviewed by the CIRB/External IRB as part of local context.

When Relying Upon another Organization's IRB. Investigators are permitted to request the reliance of an outside IRB. A signed reliance agreement must be in place prior to the start of any study approved by an external IRB. The local investigator must still submit a CIRB application to the IRB for review and approval. The CIRB application contains information about the local principal investigator and conflict of interest issues. This submission will include a CIRB application, a copy of the signed reliance agreement, CVs, Attachment Cs, current CITI certificates for all local investigators. The submission must also include a copy of the study approval letter, consent, and protocol from the external IRB. The IRB Chair will review and approve the submission to ensure that it complies with institutional policy and local context issues have been addressed.

The responsibilities of the CIRB/External IRB are to:

- 1) Perform initial reviews of new protocols, discuss any issues with the lead organization and study chair, and make a final decision of approval or disapproval of the protocol;
- 2) Maintain and make accessible to MU the CIRB/External IRB application, protocol review, letters to study chairs, approvals and disapprovals, and minutes of the CIRB/External IRB meetings;
- 3) Carry out Continuing Reviews, reviews of Serious Adverse Events, reviews of protocol amendments, reviews of Data Safety Monitoring Board (DSMB) reports, and reviews of any other documents submitted by the lead organization or study chair;
- 4) Maintain an OHRP approved Federalwide Assurance (FWA) for human subjects research;
- 5) Maintain a Board membership that satisfies the requirements of 45CFR46 and provide special expertise as needed from Board members or consultants to adequately assess all aspects of each protocol;
- 6) Notify MU immediately if there is ever a suspension or restriction of the CIRB's/External IRB's authorization to review protocols; and
- 7) Notify MU of any policy decisions or regulatory matters that might affect the institution's reliance on CIRB/External IRB reviews or performance of the research at MU.

The responsibilities of MU are to:

- 1) Ensure the safe and appropriate performance of the research at its institution. This includes, but is not limited to, monitoring protocol compliance, any major protocol violations, and any serious adverse events occurring at the institution, and providing a mechanism by which complaints about the research can be made by local study subjects or others (generally the consent form). Any actions taken as a result of problems that are identified in these areas should be shared with the CIRB/External IRB and reported as required by the procedures established by the protocol's lead organization;
- 2) The MU ORI will provide the CIRB/External IRB with requested information about local requirements or local research context issues relevant to the IRB's determination, prior to IRB review.
- 3) Ensure that the investigators and other staff who are conducting the protocol are appropriately qualified and meet the institution's standards for eligibility to conduct research;
- 4) Notify the CIRB/External IRB immediately if there is a suspension or restriction of a local investigator that utilizes their CIRB/External IRB;

- 5) Provide to the CIRB/External IRB and keep current the names and addresses of local contact persons who have authority to communicate for the local IRB, such as the local IRB administrator;
- 6) Establish a procedure by which the MU IRB will receive and review the CIRB/External IRB materials for protocols to be performed at the local institution. For each CIRB/External IRB reviewed protocol that is submitted to the local IRB by a local investigator;
 - (a) Review the CIRB's/External IRB's approval letter;
 - (b) Ensure that institutional educational and financial conflict of interest forms are complete and if any conflict resolution is required that it is addressed in accordance with institutional COI policy and reported by ORI to the CIRB/External IRB;
 - (c) Track studies on the IRB system approved by the institution.
- 7) Maintain an OHRP approved Federalwide Assurance (FWA) for human subjects research;
- 8) Maintain a human subjects protection program, as required by the DHHS OHRP;
- 9) Ensure that investigators receive proper initial and continuing education on the requirements related to human subjects protections;
- 10) Maintain compliance with any additional state, local, or institutional requirements related to the protection of human subjects.

When MU IRB is Serving as the IRB for Another Organization:

- The IRB application or other materials must contain a description of any laws relevant to the study being reviewed by the IRB, when research is conducted in another state or country.
- Information about relevant laws may be provided in a memorandum of understanding, research site agreement, local context form, or other ways.
- Requests to review the addition of research sites to a previously approved protocol requires that it be submitted as a separate protocol.
- If the IRB application or Attachment C indicates a conflict of interest that has already received a management plan at another institution, then a copy of that management plan must be submitted with the protocol (Note: that institution must have a COI policy consistent with the provision of 42 CFR Part 50, Subpart F). If there is a conflict of interest that has not be addressed at another institution then the investigator has two choices:
 - If the other institution has a COI policy consistent with the provision of 42 CFR Part 50, Subpart F, then they can address the conflict and the results submitted with the protocol, or
 - If the other institution does not have a COI policy consistent with the provision of 42 CFR Part 50, Subpart F, then the MU Conflict of Interest policy must apply and those results provided to the other organization.

When Sharing Oversight of Research:

When sharing oversight of research, the respective responsibilities of each organization must be determined through a written agreement or use MU policy and procedures. The following responsibilities must be defined:

- Ensuring concordance between any applicable grant and the IRB application.
- Reviewing potential non-compliance, including complaints, protocol deviations, and results of audits:
 - Identifying which organization is responsible for deciding whether each allegation of noncompliance has a basis in fact.
 - Identifying which organization's process is used to decide whether each incident of noncompliance is serious or continuing.
 - Obtaining management plans for investigator and research staff conflicts of interest. If the relying organization maintains responsibility for this issue, the management plan must be provided to the IRB in a timely manner prior to the decision by the IRB.
- Managing organizational conflict of interest related to the research.
- Ensuring that, should termination of a reliance agreement occur, one of the parties clearly is responsible for continued oversight of active studies until closure or a mutually agreed upon transfer of the studies.

When following DHHS and FDA regulations. The following must be added to written materials:

A written agreement must define the responsibilities of the relying organization and reviewing IRB, including but not limited to:

- Determining whether the relying organization applies its FWA to some or all research, and ensuring the IRB review is consistent with requirements in the relying organization's FWA.
- Determining which organization is responsible for obtaining any additional approvals from DHHS when the research involves pregnant women, fetuses, and neonates; or children; or prisoners.
- Determining which organization is responsible for reporting serious or continuing non-compliance; unanticipated problems involving risks to subjects or others; and suspensions or terminations of IRB approval.
 - Reporting may be done by the reviewing IRB, the relying organization, or jointly, but must be defined in policies or a written agreement.
- A description of the process to ensure IRB approval is obtained when the organization is responsible for a multi-site research study outside the United States that is not required to follow requirements for single IRB review.
- A description of the process used by the awardee organization to ensure authorization agreements are in place, and that documentation is maintained.
- A description of which organization is responsible for meeting additional certification requirements, such as Certificates of Confidentiality or the NIH Genomic Data Sharing Policy.

- A description of the process to document the rationale for not relying upon a single IRB review in accordance with NIH policy on exceptions from single IRB review.

PROCEDURES:

The Office of Human Research Protection (OHRP) Policy and Guidance standards states that when an institution holding an FWA wishes to avoid duplication of effort, in accordance with DHHS regulations at 45CFR46.114, by relying upon the IRB review of another Assurance-holding institution:

- 1) The review arrangement must be approved in writing by the appropriate officials of the institutions involved.
- 2) The institution relying upon another institution's IRB has a responsibility to ensure that the particular characteristics of its local research context are considered.

When following DoD requirements. DoD institutions collaborating with non-DoD institutions may rely on a collaborating non-DoD institution's IRB if the following conditions are met:

- Each institution engaged in non-exempt human participant research must have a current federal assurance of compliance.
- The involvement of DoD personnel in the conduct of the research is secondary to that of the non-DoD institution.
- The DoD institution, non-DoD institution, and the non-DoD institution's IRB have a written agreement defining the responsibilities and authorities of each organization in complying with all legal requirements. This agreement must be approved by the DoD component prior to the DoD institution's engagement in the research.

Steps for Protocol Submission for Total Reliance Studies: The CIRB total reliance studies (i.e. NCI CIRB) will be submitted on IRBNet using the IRB#1 CIRB Application form. The application package must also include: a copy of the CIRB approval letter or study specific worksheet, current CITI educational course completion certificates for the principal investigator and all co-investigators and an Attachment C for all co-investigators. The IRB#1 Coordinator will review the submission and provide administrative acknowledgement once all items are received, reviewed and determined to be complete.

Note: *The MU IRB approval stamp will not be included on any CIRB approved consent form since MU is not the IRB of record for these studies.*

Amendments: Study specific amendments will not need to be submitted to the MU IRB. However, if the amendment includes the addition of research team members then a submission to the MU IRB will be required to ensure education and conflict of interest requirements are met.

Continuing Reviews: The Continuing Review for CIRB studies will be conducted to correspond with the study expiration date set forth by the CIRB. The continuing review submission to ORI will

include the continuing review request form along with current CITI educational certificates. The IRB#1 Coordinator will review the submission and provide administrative acknowledgement once all items are received, reviewed and determined to be complete.

Closure of CIRB Studies: Once the CIRB study has been closed, using the procedures set forth by each CIRB, the investigator must notify the MU IRB of the closure by submitting a Closure Request on IRBNet. The IRBNet user manual contains step-by-step procedures for a closure submission.

When Relying upon an IRB that is not AAHRPP-accredited. When relying upon an IRB that is not AAHRPP-accredited the following must be applied:

- The process to evaluate whether research is being reviewed appropriately and complies with applicable law and regulations.
- Criteria describing the extent of the review to confirm compliance with the organization's ethical standards and with applicable law and regulations.
 - The extent of the review of the non-accredited IRB can vary, depending upon the level of risk to subjects in the research.

When additional reviews relevant to the HRPP are conducted by an external organization, including but not limited to biosafety review, radiation safety review, recombinant DNA research review, human stem cell research review, and conflict of interest review the following must be applied:

- How the review is documented and communicated to the IRB or other relevant part of the HRPP.
- The process for the relying organization to inform the external organization of circumstances when the external review must take into account additional regulatory requirements, for example, those of DoD or DoJ.
- Education for investigators when using these additional reviews.

Chapter 6 - Complaints, Non-Compliance, and Regulatory Improprieties

PURPOSE: To provide guidance in handling complaints, non-compliance, and regulatory improprieties in research.

POLICY: To be responsive and sensitive to the complaints of our human subjects and others and to resolve complaints in a positive and timely manner. This policy preserves the rights of the research subjects to lodge complaints and to be assured that complaints will be taken seriously. This policy also covers the issues of handling non-compliance and regulatory improprieties. Non-compliance and improprieties with regulations as well as violations of safety policies will not be tolerated and will be dealt with according to federal regulations.

NOTE: All complaints, non-compliance, and regulatory improprieties must be reported to the IRB/Director ORI within 5 business days of becoming aware of the matter. (For VA studies also see the Hershel Woody Williams VAMC Reporting SOP for other reporting requirements.)

DEFINITIONS:

Non-Compliance is failure to follow the regulations, the requirements of VHA Handbook 1200.05, or the requirements and determinations of the IRB. Examples of non-compliance may include the following:

- Failure to obtain IRB limited review approval for Exempt studies.
- Inadequate or non-existent procedures for the informed consent process.
- Failure to report adverse events or protocol changes.
- Failure to provide ongoing progress reports or closure confirmation upon completion of Full Board studies and Expedited studies that require a continuing review.
- Enrollment of subjects that fail to meet the inclusion or exclusion criteria of the protocol, which in the opinion of the IRB Chair or convened IRB, increase the risk to the subject.

Serious Non-Compliance is an action or omission in the conduct or oversight of research involving human subjects that affects the rights and welfare of participants, increases risks to participants, decreases potential benefits or compromises the integrity or validity of the research. Examples of serious non-compliance may include the following:

- Conducting non-exempt research without IRB approval.
- Enrollment of research subjects while study approval has lapsed.
- Serious protocol deviations that may place subjects at risk from the research.

Continuing Non-Compliance is a pattern of non-compliance that, in the judgment of the IRB Chair or convened IRB, indicates a lack of understanding of the regulations or institutional requirements that may affect the rights and welfare of participants, would have been foreseen as compromising the scientific integrity of a study such that important conclusions could no longer be reached, suggests a

likelihood that non-compliance will continue without intervention, or frequent instances of minor non-compliance. Continuing non-compliance also includes failure to respond to a request to resolve an episode of non-compliance.

RESPONSIBILITIES:

The Director, Office of Research Integrity (ORI) is responsible for investigating all non-compliance issues as well as any improprieties involving IRB members, investigators, or their staff. These issues will be handled in a timely manner, assuring protection of human subjects is of prime importance, and holding any violators accountable to the applicable regulation. The Director, ORI will be responsible for providing written documentation of the resolution of the violation and will make a determination for every allegation of non-compliance as to whether the allegation has a basis in fact. All non-compliance, no matter how minor, will be evaluated by the Director, ORI to determine whether it is possibly serious or continuing. The Director, ORI will evaluate all non-compliance that is neither serious nor continuing to determine whether a management plan is appropriate. The Director, ORI will report serious or continuing non-compliance to the IRB Chair, the Institutional Official (Vice President for Research) and regulatory agencies as described in the Reporting Policy (Chapter 22).

The IRB Chairperson is responsible for investigating all human subjects' complaints, for finding a suitable resolution, and for providing a response to the complaints in a timely manner. The Chairperson and the IRB members are responsible for adhering to all applicable federal regulations, especially in conflict of interest situations. They are responsible for making investigators aware of their responsibilities of taking human subjects' complaints seriously and responding to them in a timely manner. They are also responsible for making investigators aware of the repercussions of non-compliance and improprieties.

IRB Members are expected to immediately report any instances of undue influence to the Director, ORI. The Director, ORI is responsible to investigate the allegations and take corrective action.

The Principal Investigator (PI) and his staff are responsible for complying with all federal regulations concerning their research and research subjects. Investigators and research staff must promptly report all non-compliance to the IRB. They are responsible for the safety of all human subjects enrolled in their studies. The investigators will hear complaints and try to resolve them prior to the complaint being filed with the IRB Chairperson.

The IRB Coordinator is responsible for receiving complaints and issues of non-compliance or improprieties and is responsible for conveying the information to the Director or IRB Chairperson in a timely manner. The IRB Coordinator will maintain a log of all complaints, violations of compliance, and improprieties. The IRB Coordinator will also maintain a copy of the complaints as well as the Director's/Chairperson's resolution of the complaint.

PROCEDURES:

A. Complaints. A human research subject may lodge a complaint with either the principal investigator (PI) or with the Office of Research Integrity. Each complaint will be reviewed to

determine if possible non-compliance exists. If the PI receives the complaint first, he will make every effort to resolve the complaint prior to contacting the Research Office. However, the research subject may want to address the complaint(s) or inquiries about a research project by telephone, in writing, or in person to the Office of Research Integrity (ORI). Since each IRB-approved Informed Consent document includes the IRB Chairperson's/ORI telephone number (304-696-7320/4303) this may be the subject's primary point of contact. The ORI staff person receiving the complaint or allegation will establish a complaint file, including the following information:

- 1) Subject's name, address, and phone number. (NOT MANDATORY: only if the caller is willing to provide this information. A caller can report an incident anonymously; however, the caller will be advised that a thorough review may not be possible, and that, without this information, follow-up responses to the subject are not feasible.)
- 2) Study protocol title (or acronym) and Principal Investigator's name.
- 3) Date(s) of the incident.
- 4) An explanation of the complaint.

The subject will be reassured that all means will be taken to review the circumstances and appropriate measures will be taken to address the issue as required. Furthermore, the subject will be informed that a response to him or her will be forthcoming as rapidly as possible (providing that contact information is given) but no later than 14 days from the receipt of the complaint.

A copy of the complaint is forwarded to the IRB Chairperson. Within three working days after receipt, the Chairperson will explore the allegation with the Director ORI and, if warranted, identify an IRB member(s) most appropriate to review the allegations or concerns. If an IRB member review is warranted, the identified IRB member(s) will investigate the allegation(s) and prepare a written report addressing the allegation and making recommendation(s) for resolution or remedial action. The final report will be submitted to both the IRB Chairperson and Director ORI within 10 working days after receiving the assignment, which will ensure that an appropriate response to each complaint or allegation is prepared. The Chairperson will report at the following IRB meeting the action(s) taken and, if necessary, submit a report to the appropriate officials and agencies. The Director, ORI will make every effort to contact the individual who submitted the complaint or allegation to determine the level of satisfaction achieved and allow additional comments. If applicable, the Director will report these findings to the IRB.

The complaints will be handled in a confidential manner. Access is limited to only those employees with a responsibility that requires knowledge of the complaint. (Further actions are outlined in Section D below)

All complaints will be reviewed by the IRB Chair under the policy and procedures for unanticipated problems involving risks to participants or others for a determination as to whether the complaint is an unanticipated problem involving risks to participants or others, and if so, will require review by the convened IRB.

B. Compliance/Non-compliance. All Non-Compliance determined to be serious or continuing will be reviewed by the convened IRB. Each IRB member will receive a copy of the complete IRB study file for that particular study along with all correspondence related to the non-compliance. The range of actions that can be taken by the IRB are as follows (but not limited to these actions):

- Modification of the research protocol.
- Modification of the information disclosed during the consent process.
- Providing additional information to past participants.
- Notification of current participants when such information may relate to participants' willingness to continue to take part in the research.
- Requiring current participants to re-consent to participation.
- Modification of the continuing review schedule.
- Monitoring of the research.
- Monitoring of the consent.
- Suspension of the research.
- Termination of the research.
- Referral to other organizational entities.

The IRB will monitor performance of specific compliance issues and any non-compliance issues brought to the IRB's attention. Periodic audits will be conducted through a random sampling of the specific compliance issue being monitored.

When investigator non-compliance issues are identified, the Director of Office of Research Integrity will be notified and will receive a copy of the non-compliance allegation. The Director, or designee, will promptly investigate the allegation of non-compliance and corrective action will be taken. The Director will make every effort to correct the issue(s) at the administrative level. Within three working days after receipt, the Director, or designee, will explore the allegation and identify the individual(s) most appropriate to respond to the allegations/concerns. The identified responsible individual(s) will investigate the allegation(s) and prepare a written report addressing the allegation(s) and making recommendation(s) for resolution/remedial action or disciplinary action, if appropriate. The final report will be submitted to the Director within 10 working days after receiving the assignment. The Director, or designee, will ensure appropriate response to each complaint/allegation is taken. The Director will report at the following IRB meeting the action(s) taken and if necessary, submit a report to the appropriate officials and agencies.

Allegations of serious non-compliance will be reported immediately to the IRB Chairperson, the Director ORI, and to the Vice President for Research.

When Following VA Regulations. Serious or continuing non-compliance must be reported to:

- The Office of Research and Development, if VA-funded.
- The Regional Office of Research Oversight.

- A research compliance officer identifying serious or continuing noncompliance, during an informed consent or regulatory audit, must report the noncompliance to the MCD, the associate chief of staff for research and development, the Research and Development Committee, and the IRB as soon as possible but no later than five business days after becoming aware of the noncompliance.

C. Regulatory Improprieties in Research. All instances of improprieties in research will be reported to the Director, ORI. Each instance of alleged impropriety will be evaluated on a case-by-case basis. All effort will be made to correct the impropriety at the administrative level. If the impropriety involves potential harm to others or significant property damage, the appropriate institution officials will be notified for immediate action pending a formal inquiry. (Further actions are outlined in Section D.)

D. Further Actions. The ORI Director or the designee, as appropriate, will conduct an initial review to determine the nature of the complaint, non-compliance issue, or impropriety. During this review, every effort will be exercised to maintain the confidentiality of all parties involved. The Director will evaluate the facts gathered and take appropriate action. Dependent upon the nature of the event or circumstances, certain actions may occur:

- 1) Further inquiry may be initiated.
- 2) Administrative action may be taken (i.e. suspension or termination of the study).
- 3) Details and recommendations forwarded to the appropriate committee Chairpersons (e.g., IRB, Radiation, or Safety) for consideration in their committees, and action.
- 4) Details and recommendations forwarded to the appropriate Department Chairperson for action.
- 5) Details and recommendations forwarded to the Vice President for Research, Provost, University General Counsel, or the President for action.
- 6) Details and recommendations forwarded to the appropriate officials at affiliated institutions for notification, action, and follow-up, if applicable.
- 7) Other actions as deemed appropriate.

The final course of action is entirely dependant upon the nature, severity, and degree of seriousness of the findings. For example, the IRB may require special monitoring of the consent process by an impartial observer (consent monitor) to reduce the possibility of coercion and undue influence by an investigator or his staff.

The Director, ORI will report to institutional officials and regulatory agencies in accordance with Chapter 22 of this SOP.

When Following VA Regulations. The following procedures and timeframes apply:

- IRB review of apparent serious or continuing non-compliance.
 - Should the IRB determine that the reported incident constitutes serious non-compliance or continuing non-compliance, within five business days after the determination, the IRB chair or designee must provide a written report of the determination directly to:
 - MCD.
 - Associate chief of staff for research.
 - Research and Development Committee.
 - The RCO, if the apparent serious or continuing non-compliance was identified by an RCO audit, regardless of outcome.
 - Other relevant research review committee.
 - Unless the non-compliance has already been reported, within five business days after receiving such notification, the MCD must report the determination to:
 - The appropriate Office of Research Oversight research officer.
 - The VISN director.
 - Office of Research Development.
 - An initial report of an IRB determination that serious non-compliance or continuing non-compliance occurred is required, even where the determination is preliminary, or disposition of the matter has not been resolved at the time of the report.
 - The IRB must reach a determination that serious or continuing non-compliance did (or did not) occur within 30-45 days after receiving a report of apparent non-compliance.
 - 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 non-compliance must be completed within 120-180 days after the IRB's determination, unless remediation requires substantial renovation, fiscal expenditure, hiring, or legal negotiations.

Chapter 7 - Confidentiality

PURPOSE: To provide guidance on issues dealing with privacy and confidentiality of human subjects.

POLICY: To protect the privacy and confidentiality of the human research subjects to the maximum extent possible within the constraints of the regulations and reasonable means possible. To make reasonable efforts to limit the use and disclosure of and request for protected health information to the minimum necessary to accomplish the intended purpose.

SCOPE: This policy covers human subjects participating in biomedical, behavioral, clinical or other types of research protocols.

RESPONSIBILITIES:

IRB Chairperson and IRB members – The IRB Chairperson and members are responsible for ensuring privacy and confidentiality concerns are addressed when the protocol is reviewed. Any deficiencies in privacy or confidentiality identified during the review will be addressed prior to the IRB's approval of the protocol.

Principal Investigator and staff – The researchers are responsible for protecting the privacy and confidentiality of the human subjects participating in their research protocol. Certificates of Confidentiality do not take the place of good data security. Researchers are responsible for taking appropriate steps to safeguard research data and findings. Unauthorized individuals must not access the research data or learn the identity of research subjects.

IRB Coordinator – The IRB Coordinator is responsible for keeping any paper copies of the research protocols secured in the Research Office and for maintaining a log of who accesses these protocols.

PROCEDURES:

Safeguarding Confidentiality. When information linked to individuals will be recorded as part of the research design, the IRB ensures that adequate precautions will be taken to safeguard the confidentiality of the information. The IRB and researchers must be familiar with techniques for protecting confidentiality.

- 1) When the IRB reviews research in which the confidentiality of data is a serious issue, at least one IRB member (or consultant) familiar with the strengths and weaknesses of the different mechanisms available will be present. The Chairperson or his/her designee will identify the appropriate member or consultant.

- 2) The IRB can waive documentation of consent when a study meets the requirements set forth in 45CFR46.116.
- 3) Methods for ensuring confidentiality are coding of records, statistical techniques, limiting access to the records, and physical or computerized methods for maintaining the security of stored data.
- 4) Human subjects must be informed of the extent to which confidentiality of research records will be maintained.
- 5) Federal officials have the right to inspect and copy research records, including consent forms and individual medical records, to ensure compliance with the rules and standards of their programs. The provisions of the Privacy Act of 1974 protect identifiable information obtained by Federal officials during such inspections.

Other methods of safeguarding confidentiality could include:

- physical locks
- electronic passwords
- inter-file linkage
- ethical editing of qualitative descriptions
- data brokering

Department of Justice Research. When following Department of Justice regulations the following applies:

- For National Institute of Justice (NIJ) funded research:
 - All projects are required to have a privacy certificate approved by the NIJ Human Subjects Protection Officer.
 - All researchers and research staff are required to sign employee confidentiality statements, which are maintained by the responsible researcher.
- For research conducted with the Bureau of Prisons:
 - A non-employee of the Bureau may receive records in a form not individually identifiable when advance adequate written assurance that the record will be used solely as a statistical research or reporting record is provided to the agency.
 - Except as noted in the consent statement to the participant, the researcher must not provide research information that identifies a participant to any person without that participant's prior written consent to release the information. For example, research information identifiable to a particular individual cannot be admitted as evidence or used for any purpose in any action, suit, or other judicial, administrative, or legislative proceeding without the written consent of the individual to whom the data pertain.
 - Except for computerized data records maintained at an official Department of Justice site, records that contain non-disclosable information directly traceable to a specific person may not be stored in, or introduced into, an electronic retrieval system.
 - If the researcher is conducting a study of special interest to the Office of Research and Evaluation (ORE) but the study is not a joint project involving ORE, the researcher may be asked to provide ORE with the computerized research data, not identifiable to

individual participants, accompanied by detailed documentation. These arrangements must be negotiated prior to the beginning of the data collection phase of the project.

Certificates of Confidentiality (CoC). Where research involves the collection of highly sensitive information about individually identifiable subjects, the IRB may determine that special protections are needed to protect subjects from the risks of investigative or judicial processes. In such situations, the IRB may require that an investigator obtain a Department of Health and Human Services (DHHS) Certificate of Confidentiality (CoC). For studies not funded by DHHS, if there is an Investigational New Drug Application (IND) or an Investigational Drug Exemption (IDE), the sponsor can request a CoC from the FDA. The CoC was developed to protect against the involuntary release of sensitive information about individual subjects for use in Federal, state, or local civil, criminal, administrative, legislative, or other legal proceedings. Certificates constitute an important tool to protect the privacy of research study subjects.

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.

The CoC does not prohibit voluntary disclosure of information by an investigator, such as voluntary reporting to local authorities of child abuse or of a communicable disease. In addition, the CoC does not protect against the release of information to VA, DHHS or FDA for audit purposes. Consequently, the IRB will require that these conditions for release be stated clearly and explicitly in the informed consent document.

Certificates of Confidentiality are generally effective on the date of issuance or upon commencement of the research project if that occurs after the date of issuance. The expiration date should correspond to the completion of the study. The Certificate will state the date upon which it becomes effective and the date upon which it expires. A Certificate of Confidentiality protects all information identifiable to any individual who participates as a research subject (i.e., about whom the investigator maintains identifying information) during any time the Certificate is in effect. The protection afforded by the Certificate is permanent. All personally identifiable information obtained about subjects in the project while the Certificate is in effect is protected in perpetuity.

Subjects may disclose information to physicians or other third parties. They may also authorize in writing the investigator to release the information to insurers, employers, or other third parties. In such cases, researchers may not use the Certificate to refuse disclosure. However, if the researcher intends to make any voluntary disclosures, the consent form must specify such disclosure.

Certificates do not authorize researchers to refuse to disclose information about subjects if authorized DHHS personnel request such information for an audit or program evaluation. Neither can researchers refuse to disclose such information if it is required to be disclosed by the Federal Food, Drug, and Cosmetic Act.

For VA studies, if information about the subject's participation will be included in the VA medical record, information must be given to the prospective subjects as part of the informed consent process that information regarding study participation will be included in the medical record.

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 would be used or disclosed, regardless of whether or not a Certificate is in effect.

When Following DHHS Regulations for CoC. When following DHHS regulations the following is a description of the requirements for obtaining a certificate of confidentiality:

- Research is automatically covered by a certificate of confidentiality whenever the study is funded in whole or in part by the NIH and involves identifiable, sensitive information.
 - Sensitive Personal Identifying Information (PII) is defined as information that if lost, compromised, or disclosed could result in substantial harm, embarrassment, inconvenience, or unfairness to an individual.
- The following are examples of research automatically covered by a certificate of confidentiality:
 - Biomedical, behavioral, clinical or other research, including exempt research, except where the information obtained is recorded in such a manner that human subjects cannot be identified or the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects.
 - The collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual.
 - The generation of individual level, human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained.
 - Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.
- Investigators may also apply for a certificate of confidentiality for non-federally funded research.
- When research is covered by a certificate of confidentiality, investigators:

- May not disclose or provide, in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- May not disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research.
- May disclose information only when:
 - Made for the purposes of other scientific research that is in compliance with applicable federal regulations governing the protection of human subjects in research.
- When research is covered by a certificate of confidentiality, investigators must inform subjects (for example, in the consent document) of the protections and limitations of certificates of confidentiality.
 - For studies that were previously issued a Certificate and notified subjects of the protections provided by that Certificate, NIH does not expect subjects to be notified that the protections afforded by the Certificate have changed, although IRBs may determine whether it is appropriate to inform subjects.
 - If part of the study cohort was recruited prior to issuance of the Certificate, but are no longer actively participating in the study, NIH does not expect subjects consented prior to the change in authority, or prior to the issuance of a Certificate, to be notified that the protections afforded by the Certificate have changed, or that subjects who were previously consented to be re-contacted to be informed of the Certificate, although IRBs may determine whether it is appropriate to inform subjects.
- Investigators conducting NIH-supported research covered by a certificate of confidentiality must ensure that if identifiable, sensitive information is provided to other investigators or organizations, regardless of whether or not the research is federally funded, the other investigator or organization must comply with applicable requirements when research is covered by a certificate of confidentiality.
- Investigators conducting research covered by a certificate of confidentiality, even if the research is not federally funded, must ensure that if identifiable, sensitive information is provided to other investigators or organizations, the other investigator or organization must comply with applicable requirements when research is covered by a certificate of confidentiality.

Privacy. Researchers have a duty to respect the privacy of prospective subjects. That is, the researcher allows the research subject to determine when, how, and to what extent information about him or her is communicated to others. Since confidentiality deals with a person's personal data,

privacy deals the individuals themselves. Researchers usually protect an individual's right to privacy by obtaining free and informed consent before collecting personal information about him or her. The act of contacting potential subjects to seek free and informed consent to access private information may constitute a breach of privacy if the investigator does not have access to such individuals in the course of his or her usual professional activities. In general, someone the research subject would think has a reason to know why he or she might participate in the study should be the first to approach the research subject.

Research Office Files. The Office of Research Integrity (ORI) personnel are bound by all legal and ethical requirements to protect the rights of human subjects, including the confidentiality of information that can be identified with a person. IRB records are maintained on our electronic submission system IRBNet. Any paper copies of IRB records are kept secure in locked filing cabinets in the ORI. Access to IRB records is limited to the Director, ORI, the IRB Chairperson, IRB members, IRB Coordinator, ORI staff, authorized Marshall University representatives, and officials of Federal and state regulatory agencies, including the Office for Human Research Protections (OHRP), and the Food and Drug Administration (FDA). Research investigators are provided reasonable access to files related to their research. All other access to IRB records is limited to those who have legitimate need for them, as determined by the Director, ORI. Appropriate accreditation bodies are provided access as needed.

Investigator's Files. To maintain the confidentiality of subjects, no records with the subject's name or SSN should leave investigator's files or the usual location (e.g. medical record) without a reason, which cannot be otherwise met. Unnecessary risks to subject privacy and confidentiality can be avoided by reviewing consent documents in the investigator's files rather than taking them to another location. Reports of audits of investigator's files can be made for the ORI administration or IRB files, which document the oversight, yet do not have identifiers.

Chapter 8 - Conflict of Interest (Investigator/Staff)

PURPOSE: To establish the guideline for managing conflict of interest in research involving investigators and research staff.

POLICY: To manage, reduce, or eliminate potential or real conflicts of interest (e.g. financial, relational, or institutional) in approved research. This policy covers the investigators and their staff to ensure that they report any conflict of interest and ensure that financial or other incentives do not negatively impact the collection, analysis and interpretation of data, scientific objectivity and integrity, and ultimately the public trust in the research.

SCOPE: This policy covers all investigators and research staff.

DEFINITIONS:

Conflict of Interest is defined as any situation in which financial or personal obligations may compromise or present the appearance of compromising an individual's or group's professional judgment in conducting, reviewing, or reporting research. Conflict of interest is defined as any situation in which financial or personal obligations may compromise or present the appearance of compromising an individual's or group's professional judgment in conducting, reviewing, or reporting research. Conflict of interest may arise because the intellectual property involved in many research discoveries, industry academic partnerships and pharmaceutical or biotech companies may offer researchers or staff incentives for conducting trials or enrolling subjects.

Immediate family means spouse, children, parents, in-laws, and siblings.

Interest related to the research means an interest in the sponsor of the research or a product or service being tested.

RESPONSIBILITY:

Even though the **Principal Investigator (PI)** is responsible for ensuring that financial or other incentives do not negatively impact the collection, analysis and interpretation of data, scientific objectivity and integrity, and ultimately the public trust in the research all such potential conflicts of interest must be reported to the IRB.

In addition, if the investigator is also the treating physician, then the investigator must not unwittingly exert coercion or undue influence on subjects to participate in research.

An Investigator Conflict of Interest Checklist can be located on the ORI website on the Conflict of Interest webpage under Resources.

PROCEDURES:

Investigators and other research staff involved in the design, conduct, or reporting of research must disclose to the IRB at the time of initial and continuing review the following financial interests:

- 1) In the aggregate, you and your immediate family members own more than five percent (5%) or \$5,000 (whichever is less) ownership interest in any private or public corporation, partnership, proprietorship, trust, joint venture and every other business interest, including real estate used for income, and specific stocks or an interest of any amount in a non-publicly traded company that an independent observer might reasonably determine could affect or compromise, or appear to affect or compromise research. Moreover, has an ownership arrangement been entered into where the value of the ownership interests will be affected by the outcome of the research?
- 2) In the aggregate, you and your immediate family members receive more than \$100 in gifts and/or \$5,000 in honoraria, from any entity such that, to an independent observer, your research could be affected. For example, are the things of value from an entity that has a financial interest that, to an independent observer, could be related to your research? (Gifts and/or honoraria may be due to lecturing, travel, service on an advisory board, or for any other purpose not directly related to the reasonable costs of conducting the research) Moreover, has a compensation arrangement been entered into where the amount of compensation will be affected by the outcome of the research?
- 3) In the aggregate, you and/or your immediate family members receive more than \$5,000 in salary, consulting fees, wages or retainers from any entity other than the Marshall University, and the circumstances are such that, to an independent observer, your research could be affected. For example, are the things of value from an entity that has financial interests that, to an independent observer, could be related to your research? Moreover, has a compensation arrangement been entered into where the amount of compensation will be affected by the outcome of the research?
- 4) You or any member of your immediate family occupies any of the following positions: officer, director, associate, partner, member or proprietor of any corporation, sole proprietorship, partnership, or limited liability company or any other business venture, and are the circumstances such that, to an independent observer, your research could be affected. For example, is the position with an entity that has any financial interest that, to an independent observer, could be related to your research?
- 5) In the aggregate, you and/or your immediate family members receive royalty income or have a right to receive future royalties under a patent license or copyright, where your research is related to the licensed technology or work; or have other intellectual property interest where your research is related to the licensed technology or work.

- 6) You or any member of your immediate family receives non-royalty payments or entitlements to payments in connection with the research that are not directly related to the reasonable costs of research (enrollment bonuses, milestone payments, etc).
- 7) Students, interns, fellows, or other trainees under your supervision or mentorship participate in research projects in which you and/or your immediate family have a significant financial interest.
- 8) Any board or executive relationship related to the research, regardless of compensation.

Investigators and other research staff involved in the design, conduct, or reporting of research must disclose to the IRB any change in the above interests during the period for which research is approved.

If an investigator checks "Yes" in any box on the Conflict of Interest section of the IRB application, the IRB Coordinator is responsible to inform the Director, ORI. The Director, ORI is responsible for reviewing that application and, if a conflict exists, reporting this information to the Chair of the MU Conflict of Interest Committee.

Management Plans. If a conflict of interest is deemed to exist by the Chair of the MU Conflict of Interest Committee, then that conflict is to be brought before the COI committee and a convened meeting. A management plan will be discussed and, if deemed necessary, a COI Manager will be assigned. The COI Manager will work with the researcher to create a management plan to be submitted to the COI Committee for review at a convened meeting. Once the management plan is approved and implemented then annual updates will be required using the management plan update form. Any assistance required by the COI Manager or researcher will be provided by the COI Coordinator. Management of the conflict might include a retrospective review and a mitigation report if necessary. If the individual conflict involves funding or regulatory agencies then the Chair of the Conflict of Interest Committee will notify that agency in writing and make available the approved management plan.

This facility requires all faculty/staff with conflicts of interest in research submit Significant Financial Interest Disclosure (SFID) forms to ORI for review.

As one method of preventing, monitoring, managing, and resolving conflicts of interest, the IRB requires full disclosure of conflicts of interest by investigators. Full disclosure of conflicts of interest demonstrates good faith and protects the integrity of the research and the reputation of the institution and the investigator. If necessary, the IRB may require the information be included in the Informed Consent Form to inform prospective subjects about any conflict of interest.

Role conflicts (investigator/caregiver) may require particular attention for studies involving more than minimal risks. Investigators who are also a subject's caregiver should not perform the recruitment action, but rather should enlist the services of other personnel to approach potential subjects for subject recruitment to avoid undue influence on subjects to consent. The IRB will also review proposals to ensure the absence of an institutional conflict of interest (e.g., funding arrangements of institution with protocol sponsor).

The convened IRB will review all financial interests disclosed by investigators and research staff as indicated on the application form regardless of whether the Conflict of Interest Committee determined that a conflict of interest existed. The convened IRB has the final authority to decide whether the financial interest and its management, if any, allow the research to be approved.

When Following DHHS regulations:

- A financial interest consisting of one or more of the following interests of the Investigator (and those of the Investigator's spouse and dependent children) that reasonably appears to be related to the Investigator's institutional responsibilities:
 - Investigators must also disclose the occurrence of any reimbursed or sponsored travel (i.e., that which is paid on behalf of the Investigator and not reimbursed to the Investigator so that the exact monetary value might not be readily available) related to the institutional responsibilities; provided, however, that this disclosure does not apply to travel that is reimbursed or sponsored by a federal, state, or local government agency, an institution of higher education as defined at 20 U.S.C.1001(a), an academic teaching hospital, or a research institute that is affiliated with an institution of higher education.

When following VA regulations. Affiliates that serve as IRBs of record for VA facilities must use the VA financial conflict of interest form, and may not create, redraft, or change this form.

Investigator Conflict of Interest Checklist and SFID instructions can be found on the ORI website.

Chapter 9 - Conflict of Interest (IRB Members)

PURPOSE: To establish the guideline for managing conflict of interest involving the IRB members.

POLICY: To ensure that no IRB member participates in the initial or continuing review of any protocol in which the member has a conflicting interest, except to provide information requested by the IRB. The IRB members, including the Chairperson, who have conflicting interests, are required to disclose such interests and to recuse themselves from deliberations, quorum counts, and votes on the relevant protocol.

SCOPE: This policy covers all IRB members, including the Chairperson and alternate members, the Institutional Official, and the Director of the Office of Research Integrity.

DEFINITIONS:

Conflict of Interest is defined as any situation in which financial or personal obligations may compromise or present the appearance of compromising an individual's or group's professional judgment in conducting, reviewing, or reporting research. Conflict of interest is defined as any situation in which financial or personal obligations may compromise or present the appearance of compromising an individual's or group's professional judgment in conducting, reviewing, or reporting research. Conflict of interest may arise because the intellectual property involved in many research discoveries, industry academic partnerships and pharmaceutical or biotech companies may offer researchers or staff incentives for conducting trials or enrolling subjects.

Immediate family means spouse, children, parents, in-laws, and siblings.

Interest related to the research means an interest in the sponsor of the research or a product or service being tested.

RESPONSIBILITY:

The **IRB Chairperson** and **members** have the responsibility to report any situation in which financial or personal obligations may compromise or present the appearance of compromising his/her professional judgment in conducting, reviewing, or reporting research. To view the IRB Member Conflict of Interest Checklist utilize the link at the end of this chapter.

PROCEDURES:

To avoid possible conflict of interest among institutional officials, the Vice President for Research and the Director of the Office of Research Integrity, do not serve on the IRB as voting members because those who administer the research programs have access to wider knowledge, have the ability to

influence programmatic and budgetary decisions, and are in a position to possibly exert undue influence on the IRB.

The IRB members, including the Chairperson, who have conflicting interests, are required to disclose such interests and to recuse themselves from deliberations, quorum counts, and votes on the relevant protocol. Such absences are recorded in the meeting's minutes as recused and not as abstentions. The IRB is careful to keep a quorum if votes are taken during absences.

An IRB member is considered to have a conflicting interest if the IRB member, or the member's immediate family:

- 1) Have any involvement in the design, conduct, or reporting of the research.
- 2) In the aggregate, own more than five percent (5%) or \$5,000 (whichever is less) ownership interest in any private or public corporation, partnership, proprietorship, trust, joint venture and every other business interest, including real estate used for income, and specific stocks or an interest of any amount in a non-publicly traded company that an independent observer might reasonably determine could affect or compromise, or appear to affect your judgment concerning the research.
- 3) In the aggregate, receive more than \$100 in gifts and/or \$5,000 in honoraria, from any entity such that, to an independent observer, your judgment concerning the research could be affected. For example, are the things of value from an entity that has a financial interest that, to an independent observer, could be related to your judgment concerning the research? (Gifts and/or honoraria may be due to lecturing, travel, service on an advisory board, or for any other purpose not directly related to the reasonable costs of conducting the research)
- 4) In the aggregate, receive more than \$5,000 in salary, consulting fees, wages or retainers from any entity other than the Marshall University, and the circumstances are such that, to an independent observer, your judgment concerning the research could be affected. For example, are the things of value from an entity that has financial interests that, to an independent observer, could be related to your judgment concerning the research?
- 5) You or any member of your immediate family occupies any of the following positions: officer, director, associate, partner, member or proprietor of any corporation, sole proprietorship, partnership, or limited liability company or any other business venture, and are the circumstances such that, to an independent observer, your judgment concerning the research could be affected. For example, is the position with an entity that has any financial interest that, to an independent observer, could be related to your judgment concerning the research?
- 6) In the aggregate, receive royalty income or have a right to receive future royalties under a patent license or copyright, where the research study is related to the licensed technology or work; or have other intellectual property interest where the research study is related to the licensed technology or work.

- 7) Receive non-royalty payments or entitlements to payments in connection with the research study that are not directly related to the reasonable costs of research (enrollment bonuses, milestone payments, etc).
- 8) Any board or executive relationship related to the research, regardless of compensation.
- 9) Any other reason for which an IRB member believes that the member cannot objectively review the research.

Procedures for Removal of Members. Any IRB member may be removed for not acknowledging conflict of interest. In the event a member is charged with not disclosing a conflict of interest, the IRB will review the charges and a majority vote, not including the accused, may result in the recommendation to remove the member from the Board. The Director, Office of Research Integrity will make the final decision as to the removal and notify the member and the IRB, in writing.

IRB Member Conflict of Interest Checklist can be found by visiting the ORI website and then the COI webpage under Resources.

Chapter 10 - Definition of Principal Investigators and Co-Investigators

RATIONALE: The intent of this policy is to ensure the protection of human subjects participating in research by permitting only those individuals who have the proper research credentials to direct and supervise research involving human subjects.

POLICY: A Principal Investigator (PI) is that one individual who conducts a research project, under whose immediate direction research is conducted or who is the leader of a research team. Marshall University allows individuals with the proper research credentials to direct research involving human subjects by granting them Principal Investigator (PI) status. The institution has defined PIs as:

- 1) Full-Time or part-time faculty members who have been granted any of the following titles:
 - Probationary or tenured faculty (full, associate, assistant professors, or instructor)
 - Temporary faculty designated as visiting, research, clinical, extension, adjunct, or school of medicine that have a terminal degree and appropriate research credentials.
 - Emeritus faculty
- 2) Persons holding the following non-academic titles may serve as Principal Investigators on projects directly related to the mission and responsibility of their offices:
 - Director, Associate Director, Assistant Director

The Director, ORI has the authority to grant permission for an employee not meeting the above definitions to serve as a principal investigator.

Undergraduate and Graduate students and students in any professional program at Marshall University are not eligible to serve as PIs.

Residents (including Fellows) are also not eligible to serve as PIs. They are defined together under the Accreditation Council of Graduate Medical Education (ACGME).

Research projects that involve an outside agency may have restrictions that are more stringent than this Marshall University policy. In this case, the sponsor's requirements will take precedence over institutional policy for that project. For St. Mary's Medical Center, Cabell Huntington Hospital, Veterans Affairs Medical Center, and the WV Division of Criminal Justice Services, their specific Human Research Protection Program Policy will determine who can serve as a PI at their institutions.

Student Initiated Projects. For student-initiated projects, several conditions apply:

- 1) A full time faculty member, as identified under policy, must serve as the Faculty Advisor.
- 2) The Faculty Advisor will be required to manage the responsibilities as the PI under this policy.

- 3) The student will be responsible for contributing to the project under the guidance of the Faculty Advisor.
- 4) The student may be named as a Co-Investigator as long as the PI is still named as the responsible individual. The student should receive the appropriate acknowledgement.

Chapter 11 - Education and Training

PURPOSE: To establish an educational program that ensures the Institutional Review Board (IRB) members, investigators and their research staff are knowledgeable about the ethical principals and the regulations covering the rights, welfare, and protection of human subjects.

POLICY: The IRB members, investigators, and their research staff must complete the initial educational training material that constitutes certification. This training serves as an orientation to their responsibilities under the Human Research Protection Program (HRPP). In addition, recertification is required every 2 years and will rotate between the refresher course and the basic course. Additional training may be identified and required on an as-needed basis throughout the year.

SCOPE: This policy applies to the Institutional Official, IRB members, principal investigators, co-investigators, technicians, their research staff and other persons identified by the Director, Office of Research Integrity (ORI).

RESPONSIBILITIES:

Institutional Official - The Vice President for Research, as the Institutional Official, has ultimate oversight and responsibility for HRPP.

Director, Office of Research Integrity - The Director, ORI has primary responsibility for program management and ensures orientation, education, and training are provided to the IRB members, investigators, research staff and others, as deemed appropriate. The Director is held accountable for protecting the rights and safety of human subjects.

IRB Chairperson - The IRB Chairperson has the responsibility to ensure respective members complete the orientation program prior to assuming the duties as a member. In addition, the IRB Chairperson has the responsibility to ensure continual education of the members at board meetings and is held accountable for protecting the rights and safety of human subjects.

IRB members - The IRB members have the responsibility to complete the orientation program, continual educational training, and recertification, as identified by the Director, ORI. An educational topic will be conducted at each IRB meeting. IRB members are held accountable for protecting the rights and safety of human subjects.

Investigators - Principal investigators, other investigators, study coordinators, technicians, and other individuals involved with the research protocol are responsible for completion of all required orientation, education, and training identified by the Director, ORI **before** submitting protocols to the IRB. Everyone involved with the research protocol is held accountable for protecting the rights and safety of human subjects.

IRB Coordinator – The IRB Coordinator is responsible for the distribution of educational training materials, scheduling orientation and educational meetings, and monitoring educational compliance. The IRB Coordinator will conduct a semi-annual audit of training for the IRB members at the beginning of each fiscal year (July) and then again in January. The IRB Coordinator will notify the Director, ORI of anyone found not to be in compliance with the educational requirements.

PROCEDURES:

Review of the orientation educational material is required for all new IRB members, study coordinators, investigators, and their staff conducting human research protocols. Investigators and their staff will be required to submit evidence of completion of the educational requirements prior to approval of submitted protocols. Evidence of completion is accomplished by submitting the Collaborative Institutional Training Initiative (CITI) Completion Report that becomes available after achievement of a passing score in the required course.

Individual training and education sessions will be made available based on ORI Director's availability and scheduled accordingly. Emphasis will be placed on adherence to subject safety, regulatory and IRB requirements, informed consent process, and AE/SAE reporting.

Initial Orientation. An individual is considered certified after completion of the HRPP mandated orientation which includes:

- 1) **Belmont Report** - Please read the Belmont Report as it forms the basis of the Marshall University HRPP. This report can be found on the Education/Training page of the ORI website, and you must understand and be willing to abide by it.
- 2) **Human Subject Assurance Training** - Access to the web-based Collaborative Institutional Training Initiative (CITI) Course can be found on the Educational/Training page of the ORI website (or at www.citiprogram.org). Registration instructions for both IRBs are located on the IRB website. As part of the registration process you will choose the applicable IRB group (i.e., IRB#1 Medical or IRB#2 Social/Behavioral). The main menu on the CITI site contains access to all previously completed coursework and displays course title, score and completion/expiration dates. Most (not all) of the comprehensive modules within a required course are followed by a short quiz. An overall score of 80% or higher constitutes a passing score for the course. Upon achievement of the required modules, a copy of the **completion report** must be included in the protocol application.
- 3) **Standard Operating Procedures (SOP)** - IRB members and investigators will need to review the Marshall University HRPP SOP. They are responsible for familiarizing themselves with this SOP and abiding by the procedures contained therein.

The above three (3) requirements constitute initial certification. Completing the above requirements or submitting written documentation of seminars, course or other educational forums equivalent to the requirements can document recertification. The Director, ORI will determine what educational forums meet the certification requirements. The IRB members, principal investigators, and other research staff,

as identified by the Director, ORI may be required to complete additional CITI modules prior to reviewing or beginning research protocols involving certain specific topics. The ORI Director will notify the appropriate individuals at least two weeks prior to the protocol being presented at the IRB meeting to ensure sufficient time to complete the modules.

The investigator and others involved with the protocol are required to complete the educational requirements **BEFORE** submitting the research protocol to the IRB Coordinator.

Required CITI Educational Modules. The following CITI basic course modules must be completed with an overall 80% course score to fulfill the educational requirements:

IRB#1 (Medical):

- Introduction
- History and Ethics of Human Subjects Research
- Basic Institutional Review Board (IRB) Regulations and Review Process
- Informed Consent
- Records-Based Research
- Populations in Research Requiring Additional Considerations and/or Protections
- FDA-Regulated Research
- Conflicts of Interest in Research Involving Human Subjects

IRB#2 (Social/Behavioral):

- Introduction
- History and Ethical Principles – SBER
- Defining Research with Human Subjects - SBER
- The Federal Regulations - SBER
- Assessing Risk - SBER
- Informed Consent - SBER
- Privacy and Confidentiality - SBER
- Research with Children - SBER
- Internet-Based Research – SBER
- Conflicts of Interest in Research Involving Human Subjects

Education Renewal. Every 2 years, each person who continues in human subject research will be required to complete the CITI refresher/basic course. The basic and refresher courses will rotate every 2 years. The refresher modules include: History and Ethical Principals, Regulations and Process (Parts 1 & 2), and Informed Consent.

VA Training. For VAMC Research, VA training must be completed through CITI independent of MU training. The investigator and others on the study must affiliate with the VA on CITI “Huntington, WV-581” and satisfy the course requirements. Copies of the VA course completions should be submitted with the protocol for initial review by the VA Research Service and subsequent submission to the MU IRB Coordinator. Renewal of training is every 3 years. The training requirements can be found on the ORD website at <https://www.research.va.gov/pride/training/options.cfm>.

Additional Continuing Education. The CITI Course offers continuing education modules that are scenarios applicable to the required modules. Completion of the continuing education modules will be required every 2 years, however, course availability extends at any time to all desiring to expand or refresh their knowledge.

The IRB Coordinator will inform the IRB members of the continuing educational requirements of the CITI course every 24 months from the date of initial certification. Investigators and staff are required to complete the refresher course prior to submitting the continuing review request.

Handouts and educational materials on relevant regulatory and human subjects' protection issues are routinely distributed prior to or during IRB meetings via IRBNet. Institution-wide training and seminars pertinent to protection of human subjects are made a part of the continuing education program, as well.

- For Department of Defense studies there may be specific educational requirements or certification required. Any special requirements for a Department of Defense addendum will be reviewed by the IRB coordinator, then explained and distributed with the study materials. These special requirements will also be discussed as an educational topic prior to the meeting in which that study will be reviewed.

Annual Periodic Evaluation. The Director, ORI will evaluate current educational requirements and outreach activities at the beginning of each fiscal year (July).

ICH-GCP Specific Requirements:

- A qualified physician provides the medical care given to, and medical decisions made on behalf of, participants.
- The investigator provides evidence of such qualifications through up-to-date curriculum vitae or other relevant documentation requested by the sponsor, the IRB, or the regulatory authority.
- The investigator is familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current investigator's brochure, in the product information and in other information sources provided by the sponsor.
- The investigator permits monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority.
- A qualified physician (or dentist, when appropriate), who is an investigator or a co-investigator for the clinical trial, is responsible for all trial-related medical (or dental) decisions.
- The investigator ensures the accuracy, completeness, legibility, and timeliness of the data reports to the sponsor.
- If the investigator terminates or suspends its approval of the clinical trial, the investigator should promptly notify the sponsor.
- If the IRB terminates or suspends its approval of the clinical trial, the investigator should promptly notify the sponsor.
- Upon completion of the trial, the investigator informs the IRB with a summary of the trial's outcome, and the regulatory authority with any reports required.
- The available nonclinical and clinical information on an investigational product is adequate to support the proposed clinical trial.

Chapter 12 - Ensuring Prompt Reporting of Unanticipated Problems Involving Risks to Participants or Others

PURPOSE: To ensure that the organization promptly reports unanticipated problems involving risks to participants or others to the IRB, regulatory agencies, and appropriate institutional officials.

POLICY: This procedure is followed whenever a the IRB office learns problem, regardless of whether the problem is reported by the investigator or the IRB office learns about the problem by other mechanisms.

SCOPE: This policy covers all research protocols conducted within the auspices of this Institutional Review Board (IRB).

VAMC Note: For VA studies all the items listed below are to be reported within 5 business days. The time frames listed below are for non-VAMC studies. See the Hershel Woody Williams VAMC Reporting SOP for further information.

DEFINITIONS:

Adverse Event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Such events may be psychological, emotional, social, or physical and include any illness, sign, symptom, or clinically significant laboratory test abnormality that has appeared or worsened during the course of the experimental study regardless of causal relationship to the drugs and procedures under study. For observational studies (e.g., chart reviews, data base studies, surveys), deaths, life-threatening events or hospitalizations need not be reported as AEs. In addition, reports of subjects having complaints about the experimental procedures or about the conduct of the investigators may be reported as AEs.

Serious AE (SAE) or Serious Problem is an AE that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect. **These events must be reported within 5 business days.**

- 1) A serious problem in research is one that results in:
 - (a) Substantive harm or damage (or risk of substantive harm or damage) to the safety, rights, or welfare of research subjects, research staff, or others; or
 - (b) Substantive harm or damage (or risk of substantive harm or damage) to the safety or welfare of laboratory animals.

- 2) An AE or problem in research is also considered serious when medical, surgical, behavioral, social, or other intervention is needed to prevent preceding subparagraphs.

Unanticipated or Unexpected Problem is an unanticipated or unexpected problem is one that is unforeseen in terms of nature, severity, or frequency of occurrence, as documented in the protocol or other materials approved by the IRB. For human research, such materials may include the informed consent document, clinical investigators' brochure, product labeling, etc.

RESPONSIBILITY: Principal Investigator (PI) is responsible to report to the IRB the problems that require prompt reporting.

PROCEDURES:

Investigators must report to the IRB the following problems as soon as possible, but always within the described time frames:

(Note: The below items are not necessarily unanticipated problems involving risks to participants or others. These are the problems that the IRB wants promptly reported to ensure that among the reported problems will be the problems that are unanticipated problems involving risks to participants or others. The IRB, not the investigator, decides which of the reported problems are unanticipated problems involving risks to participants or others. These problems are to be reported using the IRB Adverse Event and Other Problem Report Form.)

- 1) Any harm experienced by a participant (including any adverse event) regardless of whether the event was internal (on-site) or external (off-site) and regardless of whether the event meets the FDA definition of "serious adverse event", which in the opinion of the principal investigator are both unexpected and related. Indicate that adverse events not meeting these criteria do not need to be reported.
 - (a) A harm is "unexpected" when its specificity and severity are not accurately reflected in the informed consent document.
 - (b) An harm is "related to the research procedures" if in the opinion of the principal investigator, it was more likely than not to be caused by the research procedures or if it is more likely that not that the event affects the rights and welfare of current participants).
- 2) Information that indicates a change to the risks or potential benefits of the research should be reported no later than 10 calendar days from occurrence or discovery. 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.

- 3) A breach of confidentiality should be reported no later than 10 calendar days from occurrence or discovery (including unauthorized use, loss, or disclosure of individually-identifiable subject information).
- 4) Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol should be reported no later than 10 calendar days from occurrence or discovery.
- 5) Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant should be reported no later than 10 calendar days from occurrence or discovery.
- 6) Incarceration of a participant in a protocol not approved to enroll prisoners should be reported no later than 10 calendar days from occurrence or discovery.
- 7) Event that requires prompt reporting to the sponsor should be reported no later than 10 calendar days from occurrence or discovery.
- 8) Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team should be reported no later than 10 calendar days from occurrence or discovery.
- 9) Protocol violation that caused harm to participants or others or indicates that participants or others are at increased risk of harm should be reported no later than 5 calendar days from occurrence or discovery.
- 10) DSMB reports.
- 11) Unanticipated adverse device effect (Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.)
- 12) New information that may affect adversely the safety of the participants or the conduct of the clinical trial. (*ICH-GCP compliant studies*)
- 13) Any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants. (*ICH-GCP compliant studies*)

All reported problems will be reviewed by the IRB Chair or his/her designee. The reviewer will be provided the IRB Adverse Event and Other Problem Report Form and the study file. This reviewer will determine and document whether the reported problem is an unanticipated problem involving new or increased risk of harm to participants or others based on whether the event is:

- Related (or possibly related) to the study.

- Unexpected.
- New or increased risk of harm.

If the reviewer determines that the event is an unanticipated problem involving risk to participants or others that are greater than minimal risk, he/she will require review by the convened IRB. The reviewer must also determine if immediate action is warranted (e.g., suspension of activities; notification of subjects) to prevent an immediate hazard or if no immediate action is warranted to prevent an immediate hazard prior to the IRB review. If the reviewer determines that the event is an unanticipated problem involving risks to participants or others that are minimal risk, no full board actions are required and the report will be listed as informational on the agenda.

The convened IRB will make a determination on referred unanticipated problems involving new or increased risk of harm to participants or others and the board action will be reflected in the minutes of the meeting. If the convened IRB determines that the event is not an unanticipated problem involving new or increased risk of harm to participants or others, no further considerations or actions are required. All IRB members will receive a copy of the IRB Adverse Event and Other Problem Report Form, any materials the investigator sent, the protocol and consent document (if applicable) and the reviewer's comments.

The range of actions to be considered by the convened IRB, include (but are not limited to):

- Modification of the research protocol.
- Modification of the information disclosed during the consent process.
- Providing additional information to past participants.
- Notification of current participants when such information may relate to participants' willingness to continue to take part in the research.
- Requirement that current participants re-consent to participation.
- Modification of the continuing review schedule.
- Monitoring of the research.
- Monitoring of the consent.
- Suspension of the research.
- Termination of the research.
- Referral to other organizational entities.

The Director, ORI will report to the Institutional Official (Vice President for Research) and regulatory agencies when the IRB determines that a problem is an unanticipated problem involving risks to participants or other. See Chapter 22 of this SOP for information on reporting procedures.

When Following VA Regulations:

- Serious unanticipated problems involving risks to subjects or others include:
 - 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.
 - 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 individuals, or leads to serious complications or death.
- Any VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the VA facility's research projects.
 - Any data monitoring committee, data and safety monitoring board, or data and safety monitoring committee report describing a safety problem.
 - Any sponsor analysis describing a safety problem for which action at the VA facility might be warranted.
 - 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.
 - Any problem reflecting a deficiency that substantively compromises the effectiveness of the VA facility's HRPP.
 - The unfounded classification of a serious adverse event as "anticipated" constitutes serious non-compliance.
- The unfounded classification of a serious adverse event as "anticipated" constitutes serious non-compliance.

The IRB Adverse Event and Other Problem Report Form can be found on the ORI website and in the IRBNet Forms and Templates Library.

Chapter 13 - Informed Consent

PURPOSE: To establish guidelines for conducting the informed consent process and for obtaining the consent for human subjects to participate in research activities.

POLICY: Obtaining informed consent is a process. The procedures used to obtain informed consent are designed to educate the human subject about the research project in terms that he/she can understand. Prospective subjects are given sufficient information about the research and its risks and benefits to reach an informed decision as to whether they will **voluntarily participate**. Investigators must obtain the informed consent of prospective subjects before they can be included in research. Various templates/waiver forms are available on the ORI website and in IRBNet.

SCOPE: To approve research, the IRB must determine that legally effective informed consent is sought from each prospective subject or the subject's legally authorized representative, unless the informed consent requirements can be waived or altered under federal regulations.

DEFINITIONS:

Child (DHHS/FDA): 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.

Guardian (DHHS/FDA): An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

Legally Authorized Representative (DHHS/FDA): Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research. The selection of surrogate healthcare decision makers for incapacitated patients in the absence of an advance directive will be made consistent with the provisions of West Virginia law as contained in W.V. Code § 16-30-1.

For VAMC Research: A legally authorized representative (LAR) is an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, LAR means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

Legally Authorized Representatives (LAR) in WV, Ohio, and Kentucky may consent to research on behalf of a participant only in those instances authorized by state law and MU Research Policies.

LARs include those who are:

- the judicially-appointed guardian of the person, if the guardian has been appointed and if medical decisions are within the scope of the guardianship;
- the attorney-in-fact named in a durable power of attorney, if the durable power of attorney specifically includes authority for health care decisions;
- the parent or spouse of the person;
- if the person is incompetent, an adult child of the person, or if the person has more than one (1) child, the majority of the adult children who are reasonably available for consultation;
- the nearest living relative of the person, or if more than one (1) relative of the same relation is reasonably available for consultation, a majority of the nearest living relatives.

Under WV, Ohio, and Kentucky law, the individuals who meet the DHHS and FDA definition of “guardian” include those who are:

- the judicially-appointed guardian of the child, if the guardian has been appointed and if medical decisions are within the scope of the guardianship;
- the attorney-in-fact named in a durable power of attorney, if the durable power of attorney specifically includes authority for health care decisions;
- the legally authorized representative of the child as defined above.

In order to give informed consent to treatments or procedures involved in research, a person must be legally competent to do so and be eighteen years of age or older. In West Virginia, Kentucky, and Ohio, Subpart D of 45 CFR 46 applies to all research involving individuals under the age of 18 unless the individual is emancipated under state law (i.e. by court order, marriage, or is on active military duty). These are the individuals who meet the Subpart D definition of a "child" for our research purposes in these three states.

If research is to be conducted in other states with legally authorized representatives, children, or guardians, then the investigator must provide the IRB with the state law that describes who would fall under the Subpart A of 45 CFR 46 and 21 CFR 50, 56 definitions of “legally authorized representative”, the Subpart D of 45 CFR 46 and 21 CFR 56 definitions of "children" or the Subpart D of 45 CFR 46 and 21 CFR 56 definitions of "guardian," respectively. The IRB determines whether the information is adequate and may consult legal counsel.

RESPONSIBILITIES:

The **Director, Office of Research Integrity (ORI)** or someone designed by the Director is responsible for the random monthly monitoring of the informed consent process and for auditing the informed consent documents that are maintained in the investigator’s files.

The **IRB Chairperson** and **IRB members** are responsible for ensuring that the informed consent document contains all required elements and additional elements when appropriate. They must ensure the language in the informed consent form is consistent with that in the protocol and, when applicable, in the HIPAA authorization. They are also responsible for ensuring that the informed consent process

is properly carried out by the investigator or a properly trained member of the research team. IRB Chairperson Contact Information is:

IRB#1

Henry Driscoll, M.D.
Phone: (304) 696-4303

IRB#2

Christopher LeGrow, Ph.D.
Phone: (304) 696-4303

The **Principal Investigator (PI)** is responsible for explaining the consent process, the research, and the consent form to the subject in language they can understand and for obtaining the signed consent. The PI is responsible for determining if the human subject has the legal, mental, and emotional ability to understand the consent process; otherwise, the subject's legally authorized representative must be contacted. The PI must also ensure that the informed consent process is followed, regardless of which member(s) of the research team are authorized to actually obtain the consent and that the consent is documented properly. The PI is responsible for assuring that the informed consent contains all required elements and it is approved by the **IRB prior to** utilizing the form. All informed consents should have the pages numbered and a place for the subject to initial any page that does not have a signature (i.e. Initials____). Any changes to the informed consent must also be approved by the IRB prior to utilizing the changed informed consent.

The **IRB Coordinator** is responsible for maintaining a copy of all approved informed consent documents. The Coordinator is also responsible for documentation of exceptions from Informed Consent requirements for emergency use of a test article in the IRB records, when applicable. The IRB coordinator will also ensure that the MU approval stamp includes the study number, initial approval date, expiration date and is included on all consent forms.

Note: *The MU IRB approval stamp will not be included on any CIRB approved consent since MU is not the IRB of record for those studies.*

PROCEDURES:

To approve research activities, the IRB must determine that a legally effective informed consent is sought from each prospective subject or the subject's legally authorized representative unless waiver of consent or waiver of documentation of consent is approved according to federal regulations. The IRB must determine whether consent by the subject's legally authorized representative is allowed.

Legal Counsel - for access to legal counsel for assistance in applying laws other than federal to research involving humans as participants, contact the Marshall University Office of General Counsel.

Informed Consent. Informed consent may only be sought under circumstances that provide the subject (or the legally authorized representative) with sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.
For example:

- 1) Informed consent information must be presented in language that is understandable to the subject (or the legally authorized representative).

- 2) No informed consent process may 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, Marshall University, or the University's employees or agents are released from liability for negligence, or appear to be so released.
- 3) Informed consent must be obtained **prior** to initiation of any clinical screening procedures that are performed solely for the purposes of determining eligibility for research.

General Requirement for Informed Consent (45CFR46.116(a)):

General requirements for informed consent, whether written or oral, are set forth in this paragraph and apply to consent obtained in accordance with the requirements set forth in the basic elements of informed consent, additional elements of informed consent, and the elements of broad consent as describe in this chapter. Broad consent may be obtained in lieu of informed consent as described in the Elements of Broad Consent section of this chapter only with respect to the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens. Waiver or alteration of consent in research involving public benefit and service programs conducted by or subject to the approval of state or local officials is described in this chapter. General waiver or alteration of informed consent is also described in this chapter under that title. Except as provided elsewhere in this policy:

- 1) Before involving a human subject in research covered by this policy, an investigator shall obtain the legally effective informed consent of the subject or the subject's legally authorized representative.
- 2) An investigator shall seek informed consent only under circumstances that provide the prospective subject or the legally authorized representative sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence.
- 3) The information that is given to the subject or the legally authorized representative shall be in language understandable to the subject or the legally authorized representative.
- 4) The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.
- 5) Except for broad consent as describe in this chapter:
 - (a) Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.

- (b) Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.
- 6) No informed consent may include any exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

Basic Elements of Informed Consent (45CFR46.116(b)):

Basic elements of informed consent. Except as provided in the elements of broad consent or waivers as described in this chapter, in seeking informed consent the following information shall be provided to each subject or the legally authorized representative:

- 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 that are experimental;
- 2) A description of any reasonably foreseeable risks or discomforts to the subject;
- 3) A description of any benefits to the subject or to others that may reasonably be expected from the research;
- 4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- 5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- 6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- 7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;
- 8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled; and

- 9) One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:
- (a) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
 - (b) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

Additional Elements of Informed Consent (45CFR46.116(c)):

Additional elements of informed consent. Except as provided in this chapter under Elements of Broad Consent, Waiver or Alteration of Consent in Research Involving Public Benefit and Service Programs, or General Waiver or Alteration of Consent, one or more of the following elements of information, when appropriate, shall also be provided to each subject or the legally authorized representative:

- 1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable;
- 2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or the legally authorized representative's consent;
- 3) Any additional costs to the subject that may result from participation in the research;
- 4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
- 5) A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject;
- 6) The approximate number of subjects involved in the study;
- 7) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
- 8) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and

- 9) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).
- 10) When appropriate, a statement that informs VA research subjects that they or their insurance will not be charged for any costs related to the research. (**NOTE:** *Some Veterans are required to pay copayments for medical care and services specifically related to their medical care provided by VA. These co-payment requirements will continue to apply to medical care and services that are not part of the research procedures or interventions.*)

Elements of Broad Consent (45CFR46.116(d)):

Elements of broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens. Broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens (collected for either research studies other than the proposed research or nonresearch purposes) is permitted as an alternative to the informed consent requirements in the Basic Elements of Informed Consent and Additional Elements of Informed Consent as described in this chapter. If the subject or the legally authorized representative is asked to provide broad consent, the following shall be provided to each subject or the subject's legally authorized representative:

- 1) The following information as required in 45CFR46.116(d):
 - (a) A description of any reasonably foreseeable risks or discomforts to the subject;
 - (b) A description of any benefits to the subject or to others that may reasonably be expected from the research;
 - (c) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
 - (d) 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;

and, the following two when appropriate;

- (e) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
- (f) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

- 2) A general description of the types of research that may be conducted with the identifiable private information or identifiable biospecimens. This description must include sufficient information such that a reasonable person would expect that the broad consent would permit the types of research conducted;
- 3) A description of the identifiable private information or identifiable biospecimens that might be used in research, whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or researchers that might conduct research with the identifiable private information or identifiable biospecimens;
- 4) A description of the period of time that the identifiable private information or identifiable biospecimens may be stored and maintained (which period of time could be indefinite), and a description of the period of time that the identifiable private information or identifiable biospecimens may be used for research purposes (which period of time could be indefinite);
- 5) Unless the subject or legally authorized representative will be provided details about specific research studies, a statement that they will not be informed of the details of any specific research studies that might be conducted using the subject's identifiable private information or identifiable biospecimens, including the purposes of the research, and that they might have chosen not to consent to some of those specific research studies;
- 6) Unless it is known that clinically relevant research results, including individual research results, will be disclosed to the subject in all circumstances, a statement that such results may not be disclosed to the subject; and
- 7) An explanation of whom to contact for answers to questions about the subject's rights and about storage and use of the subject's identifiable private information or identifiable biospecimens, and whom to contact in the event of a research-related harm.

Waiver or Alteration of Informed Consent in Research Involving Public Benefit and Service Programs (45CFR46.116(e)):

Waiver or alteration of consent in research involving public benefit and service programs conducted by or subject to the approval of state or local officials:

- 1) Waiver. An IRB may waive the requirement to obtain informed consent for research under General Requirements for Informed Consent, Basic Elements of Informed Consent, Additional Elements of Informed Consent of this chapter, provided the IRB satisfies the requirements of this chapter. If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens in accordance with the requirements of Elements of Broad Consent as described in this chapter, and refused to consent, an IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.

- 2) Alteration. An IRB may approve a consent procedure that omits some, or alters some or all, of the elements of informed consent set forth in Basic Elements of Informed Consent and Additional Elements of Informed Consent as described in this chapter provided the IRB satisfies the requirements of item 3 of this section. An IRB may not omit or alter any of the requirements described in the General Requirement of Informed Consent as described in this chapter. If a broad consent procedure is used, an IRB may not omit or alter any of the elements required under that section.
- 3) Requirements for waiver and alteration. In order for an IRB to waive or alter consent as described in this subsection, the IRB must find and document 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:
 - i. Public benefit or service programs;
 - ii. Procedures for obtaining benefits or services under those programs;
 - iii. Possible changes in or alternatives to those programs or procedures; or
 - iv. Possible changes in methods or levels of payment for benefits or services under those programs; and
 - (b) The research could not practicably be carried out without the waiver or alteration.

General Waiver or Alteration of Informed Consent (45CFR46.116(f)):

- 1) Waiver. An IRB may waive the requirement to obtain informed consent, as described in the previous sections, for research provided the IRB satisfies the requirements of item 3 of the Waiver or Alteration of Consent in Research Involving Public Benefit and Service Programs section above. If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens in accordance with the requirements of broad consent as described in this chapter, and refused to consent, an IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.
- 2) Alteration. An IRB may approve a consent procedure that omits some, or alters some or all, of the elements of informed consent defined in this chapter provided the IRB satisfies the requirements of item 3 of the Waiver or Alteration of Consent in Research Involving Public Benefit and Service Programs section above. An IRB may not omit or alter any of the general requirements of informed consent described in this chapter. If a broad consent procedure is used, an IRB may not omit or alter any of the elements required in the elements of broad consent.
- 3) Requirements for waiver and alteration. In order for an IRB to waive or alter consent as described in this subsection, the IRB must find and document that:
 - (a) The research involves no more than minimal risk to the subjects;

- (b) The research could not practicably be carried out without the requested waiver or alteration;
- (c) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
- (d) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
- (e) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

These findings and their justifications will be clearly documented in IRB minutes when the IRB exercises this waiver provision. This waiver provision is not applicable to research governed by FDA regulations, and the IRB cannot approve such alterations or waivers for FDA-regulated research. Under FDA regulations, if consent is not deemed feasible and thus, is not obtained, the investigator and another physician not otherwise participating in the clinical investigation must certify, in writing, the same information as outlined in the section below on “Documentation of Exceptions from informed consent requirements for emergency use of a test article.”

If the research participant meets the definition of “experimental subject” (as per DOD Directive 3216.2) a waiver of consent is prohibited unless a waiver is obtained from the Secretary of Defense. If the research participant does not meet the definition of “experimental subject” the IRB may waive the consent process.

When Following DHHS Regulations:

Waiver of Documentation of the Consent Process – Screening, Recruiting, and Determining Eligibility

- The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, or
- The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.
- The research is not regulated by the US FDA.

Waiver of Documentation of the Consent Process – Confidentiality

- The oral or written information provided to subjects includes all required and appropriate additional elements of consent disclosure.
- The IRB has determined whether the subject should be provided written information.
- The research is not regulated by the US FDA.

Waiver of Documentation of the Consent Process: Consent normally not required outside the research context

- The oral or written information provided to subjects includes all required and appropriate additional elements of consent disclosure.
- The IRB will determine whether the investigator should provide subjects with a written statement regarding the research.
- The research is not regulated by the US FDA.

Waiver of Documentation of the Consent Process: Distinct Cultural Groups

- There is an appropriate alternative mechanism for documenting that informed consent was obtained.
- The oral or written information provided to subjects includes all required and appropriate additional elements of consent disclosure.
- The IRB will determine whether the investigator should provide subjects with a written statement regarding the research.
- The research is not regulated by the US FDA.

When Following FDA Regulations:

- The IRB is allowed to waive or alter the consent process by determining that the regulatory criteria for waivers or alterations of the consent process are met.
- Written materials allow the IRB to waive the requirement to document the consent process by determining that the regulatory criteria for waivers are met.
 - When the IRB considers waiving the requirement to obtain written documentation of the consent process, policies and procedures have the IRB review a written description of the information that will be provided to subjects.

When Following DoD Requirements:

- The Assistant Secretary of Defense for Research and Engineering may waive the requirements for consent when all of the following are met:
 - The research is necessary to advance the development of a medical product for the Military Services.
 - The research might directly benefit the individual experimental subject.
 - The research is conducted in compliance with all other applicable laws and regulations.

Documentation of Informed Consent (45CFR46.117):

- 1) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written informed consent form approved by the IRB and signed (including in an electronic format) by the subject or the subject's legally authorized representative. A written copy shall be given to the person signing the informed consent form.

- 2) Except as provided in paragraph (c) of this section, the informed consent form may be either of the following:
 - (a) A written informed consent form that meets the requirements of §46.116. The investigator shall give either the subject or the subject's legally authorized representative adequate opportunity to read the informed consent form before it is signed; alternatively, this form may be read to the subject or the subject's legally authorized representative.
 - (b) A short form written informed consent form stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject's legally authorized representative, and that the key information required by §46.116(a)(5)(i) was presented first to the subject, before other information, if any, was provided. The IRB shall approve a written summary of what is to be said to the subject or the legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Only the short form itself is to be signed by the subject or the subject's legally authorized representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the subject's legally authorized representative, in addition to a copy of the short form.
- 3) Waiver of the requirement for a signed informed consent:
 - (a) An IRB may waive the requirement for the investigator to obtain a signed informed consent form for some or all subjects if it finds any of the following:
 - i. That the only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject (or legally authorized representative) will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern;
 - ii. That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context; or
 - iii. If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.
 - (b) In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects or legally authorized representatives with a written statement regarding the research.

(c) Waiver of Documentation of the Consent Process: Consent normally not required outside the research context

- The oral or written information provided to subjects includes all required and appropriate additional elements of consent disclosure.
- The IRB has determined whether the investigator should provide subjects with a written statement regarding the research.

When the Research Involves Children:

- The IRB is allowed to waive or alter the consent process by determining that the regulatory criteria for waivers or alterations of parental permission are met.
- Written materials allow the IRB to waive the requirement to document the parental permission by determining that the regulatory criteria for waivers are met.

Waiver of Parental or Guardian Permission. If the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements of the parent or guardian, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further 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. A request for this kind of waiver must be submitted in writing and included in the initial protocol packet. Marshall does not currently approve passive consent.

Consent considerations for various departments/agencies:

FDA. For FDA-regulated research the consent must inform the participant that the FDA may choose to inspect and copy medical or research records that identify individual research subjects.

- 1) When following FDA regulations there must be a statement that the results of the research will be posted on clinicaltrials.gov:
 - (a) “A description of this clinical trial will be available on <http://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.”

Department of Justice (DOJ). When following Department of Justice regulations the following applies:

- 1) For National Institute of Justice-funded research:
 - (a) The confidentiality statement on the consent form must state that confidentiality can only be broken if the participant reports immediate harm to participants or others.

- (b) Under a privacy certificate, researchers and research staff do not have to report child abuse unless the participant signs another consent form to allow child abuse reporting.
- 2) For research conducted within the Bureau of Prisons required elements of disclosure include:
 - (a) Identification of the researchers.
 - (b) Anticipated uses of the results of the research.
 - (c) A statement that participation is completely voluntary and that the participant may withdraw consent and end participation in the project at any time without penalty or prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable).
 - (d) A statement regarding the confidentiality of the research information and exceptions to any guarantees of confidentiality required by federal or state law. For example, a researcher may not guarantee confidentiality when the participant indicates intent to commit future criminal conduct or harm himself or herself or someone else, or, if the participant is an inmate, indicates intent to leave the facility without authorization.
 - (e) A statement that participation in the research project will have no effect on the inmate participant's release date or parole eligibility.

Department of Defense (DOD). Department of Defense components may have stricter requirements than the Common Rule requirements for research-related injury.

Department of Education (DOE). When following Department of Education regulations the investigator is responsible to describe the following:

- 1) A process to comply with the Family Educational Rights and Privacy Act (FERPA).
- 2) The process to grant exceptions to parental/student consent to release student records for research. This responsibility may be delegated to the IRB or another individual or component of the organization (e.g., a FERPA committee).
 - (a) An educational agency or institution may disclose personally identifiable information from an education record of a student without consent if the disclosure is to organizations conducting studies for, or on behalf of, educational agencies or institutions to:
 - i. Develop, validate, or administer predictive tests.
 - ii. Administer student aid programs.
 - iii. Improve instruction.

- 3) A school district or postsecondary institution that uses this exception is required to enter into a written agreement with the organization or researcher conducting the research that specifies:
 - (a) The determination of the exception.
 - (b) The purpose, scope, and duration of the study.
 - (c) The information to be disclosed.
 - (d) That information from education records may only be used to meet the purposes of the study stated in the written agreement and must contain the current requirements in 34 CFR 99.31(a)(6) on re-disclosure and destruction of information.
 - (e) That the study will be conducted in a manner that does not permit personal identification of parents and students by anyone other than representatives of the organization with legitimate interests.
 - (f) That the organization is required to destroy or return all personally identifiable information when no longer needed for the purposes of the study.
 - (g) The time period during which the organization must either destroy or return the information.

Education records may be released without consent under FERPA if all personally identifiable information has been removed including:

- 1) Student's name and other direct personal identifiers, such as the student's social security number or student number.
- 2) Indirect identifiers, such as the name of the student's parent or other family members; the student's or family's address, and personal characteristics or other information that would make the student's identity easily traceable; date and place of birth and mother's maiden name.
- 3) Biometric records, including one or more measurable biological or behavioral characteristics that can be used for automated recognition of an individual, including fingerprints, retina and iris patterns, voiceprints, DNA sequence, facial characteristics, and handwriting.
- 4) Other information that, alone or in combination, is linked or linkable to a specific student that would allow a reasonable person in the school community, who does not have personal knowledge of the relevant circumstances, to identify the student with reasonable certainty.

VA Additional Elements. When appropriate, VA requires one or more of the following elements of information to be provided to each subject. Also, when any of these additional elements are appropriate, VA requires them to be documented in the IRB-approved informed consent form, unless documentation of informed consent is waived.

- 1) A statement that VA will provide treatment for research related injury in accordance with 38 CFR 17.85. (**NOTE:** *VA's statutory requirements in 38 CFR 17.85 apply regardless of inclusion of the information as part of the informed consent process.*)
- 2) When appropriate, a statement that informs VA research subjects that they or their insurance will not be charged for any costs related to the research. (**NOTE:** *Some Veterans are required to pay copayments for medical care and services specifically related to their medical care provided by VA. These co-payment requirements will continue to apply to medical care and services that are not part of the research procedures or interventions.*)

Payment for Participation. The informed consent information should include a clear statement describing any payment the subject is to receive for participation, the required conditions for payment, and the payment schedule. Since federal regulations at 38 CFR 16.116(a)(8), the Common Rule, and FDA regulations all stipulate that subjects may withdraw from research at any time without penalty of loss of benefits to which they are otherwise entitled, completing the research may not be made a condition of payment. For this reason there should be a description of how payment will be prorated and calculated for subjects who withdraw early.

Limitations on dual compensation for U.S. military personnel:

- 1) Prohibits an individual from receiving pay from more than one position for more than 40 hours of work on one calendar week.
- 2) Includes temporary, part-time, and intermittent appointments.

Obtaining Consent from Non-English Speakers. Regulations require that informed consent be obtained in language that is understandable to the subject (or the subject's legally authorized representative). 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. The IRB requires that appropriately translated consent documents be submitted to the IRB for review and approval **prior** to their use in enrolling subjects. The IRB may utilize expedited review procedures in approving such documents if the English language consent document has already been approved, and the investigator attests in writing to the accuracy of the translation. When a short-form consent document is used, the short form itself must be written in a language understandable to the subject, although the summary may be in English. The translator who took part in the informed consent conference may serve as the witness.

Short Form Consent. A short form written consent is a document stating that the elements of informed consent required by 45CFR46.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed and dated by the subject or the representative. However, the witness shall sign and date both the short form and a copy of the summary, and the

person actually obtaining consent shall sign and date a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

To use the Short Form Consent you must:

- 1) Obtain IRB approval prior to using the short form consent.
- 2) Provide a summary document (i.e. the full informed consent).
- 3) Provide the short form consent document (see below sample).

These documents must accompany a new protocol application or be submitted as an amendment to an existing protocol.

The following are the signature requirements:

- 1) Ensure that the short form document is signed and dated by the subject (or the subject's legally authorized representative).
- 2) Ensure that the short summary is signed and dated by the person obtaining consent as authorized under the protocol (i.e. the oral presenter).
- 3) Ensure that the short form document and the summary document are signed and dated by a witness.

A copy of the signed and dated short form and the summary will be given to the participant or the representative.

A Short Form Consent Template is available on the ORI website and in the IRBNet library.

Understanding the Informed Consent. Human subjects are at risk of not being able to make a truly informed decision as to their desire and willingness to participate in research when he/she does not understand the informed consent. The language in the informed consent must be at the reading level of the subject.

Waiver of HIPAA Authorization. Under the Health Insurance Portability and Accountability Act (HIPAA) research use or disclosure of an individual's identifiable health information requires the individual's authorization, unless the use or disclosure is determined by the IRB to qualify for a waiver. The request form for a HIPAA waiver must be submitted with the study and approved by the IRB chair (for expedited studies) or convened board. Once it is determined that the protocol-specific findings justify granting such a waiver, the IRB approved form will be maintained in the protocol file.

New Findings and Additional Risks require changes in the Informed Consent. If additional risks are identified during the course of the research, the consent process and documentation will require revisions to inform the subjects as they are re-contacted or newly contacted. If the event is serious and unexpected, the risks section of the consent form should be revised to include the possibility and likelihood of the event. If subjects are currently enrolled in the study, a consent addendum may need

to be drafted. A revised consent form may be submitted at the time of AE reporting, if the PI believes such action is warranted prior to IRB review.

The Informed Consent should have 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 participant.

Documentation of Exceptions from informed consent requirements for emergency use of a test article. A test article is any drug, biological product for human use, medical device for human use, human food additive, and color additive, electronic product subject to FDA regulations.

FDA regulations permit the use of a test article without the informed consent of the subject (or the subject's legally authorized representative) where the clinical investigator and a physician not otherwise involved in the research certify in writing that:

- 1) The subject is confronted with an immediately life threatening emergency necessitating the use of the test article;
- 2) Informed consent cannot be obtained from the participant because of an inability to communicate with, or obtain legally effective consent from the participant;
- 3) Time is not sufficient to obtain consent from the subject's legally authorized representative;
and
- 4) There is no alternative approved or generally recognized therapy that provides equal or greater likelihood of saving the subject. If time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by an independent physician.

This written certification **must** be submitted to the IRB **within 5 working days** of the use of the test article. The Director, ORI is required to evaluate this report and communicate all findings with the IRB chair. This report will also be reviewed to determine that the circumstances of the exception followed FDA regulations.

Planned Emergency Research. This is not currently reviewed by the MU IRB.

Consent Monitoring. The IRB may require special monitoring of the consent process by an impartial observer (consent monitor) 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 also may be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project. The IRB may also require that investigators include a "waiting period" within the consent process or use devices such as audio-visual aids or tests of comprehension.

The IRB will determine who will conduct the consent monitoring and how often the monitoring will take place.

Understanding the Process of Assent. The basic consent model when working with children is that parents (or guardians) provide permission for their children (or wards) to participate in research and permission to contact the children. Children then provide assent to become subjects. Assent is a child's affirmative agreement to participate. The absence of dissent should not be construed as assent. Generally, parental permission can only override a child's dissent when the health of the child is at stake. When using an Assent form, the child signs the Assent to indicate knowledgeable agreement (assent) to participate. In addition, the parents, guardian or legally authorized representative signs and dates the full Informed Consent Document to document legal permission. There is a template of the child assent below. Keep in mind that if a participant is assented into a study and then turns 18 during enrollment in the study, that participant must then be consented to remain in the study.

Obtaining Consent/Assent from Vulnerable Subjects. There must be special consideration to protecting the welfare of vulnerable subjects, such as children, prisoners, pregnant women, mentally disabled persons, and economically or educationally disadvantaged persons. For information on the specific processes and responsibilities involved in consent/assent of vulnerable subjects, please refer to chapter 25 of this SOP.

For VAMC research the following is required:

- 1) The participant or the participant's legally authorized representative must sign and date the consent document.

For VAMC research, the informed consent for research must include information describing any photographs, video, and/or audio recordings to be taken or obtained for research purposes; how the photographs, video, and/or audio recordings will be used for the research; and whether the photographs, video, and/or audio recordings will be disclosed outside VA.

- 1) An informed consent to take a photograph, video and/or audio recording cannot be waived by the IRB.
- 2) The consent for research does not give legal authority to disclose the photographs, video, and/or audio recordings outside VA. A HIPAA authorization is needed to make such disclosures.

For VAMC research, if the investigator does not personally obtain informed consent, the investigator must delegate this responsibility in writing (e.g., by use of a delegation letter) to research staff sufficiently knowledgeable about the protocol and related concerns to answer questions from prospective subjects, and about the ethical basis of the informed consent process and protocol.

For VAMC research, investigators are responsible for creating or updating a VHA health record and creating a progress note for all research subjects (Veterans or non-Veterans) who receive research procedures or interventions as inpatients or outpatients at VA medical facilities that are either used in

or may impact the medical care of the research subject at a VA medical facility or at facilities contracted by VA to provide services to Veterans (e.g., Community-Based Outpatient Clinics or community living centers). Informed consent and HIPAA authorization documents are not required to be in the health record

ICH-GCP Consent Items. Marshall University and its affiliates have chosen **not** to incorporate the following ICH-GCP consent items to all consent forms (*ICH-GCP compliant studies only*):

- 1) Ensure the consent form explains the subject's responsibilities.
- 2) For alternative procedures or treatment that may be available to the participant, include their important potential benefits and risks.
- 3) That the monitor, the auditor, the IRB, and the regulatory authority will be granted direct access to the participant's original medical records for verification of clinical trial procedures or data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the participant or the participant's legally acceptable representative is authorizing such access.

Informed Consent Templates for both IRBs are available on the ORI website and IRBNet library.

Chapter 14 - Investigational Drugs/Devices

PURPOSE: To assure that investigators conduct research utilizing drugs, biologics, devices, diagnostics, and dietary supplements and food additives in compliance with the guidelines set forth by the Food and Drug Administration and other federal regulations as applicable.

POLICY: This policy covers the research under the auspices of this IRB and covered by FDA regulations. The FDA regulates clinical investigations (research) conducted on drugs, biologics, devices, diagnostics, and, in some cases, dietary supplements and food additives, also known as “FDA regulated test articles.” All such investigations are to be conducted in accordance with FDA requirements for informed consent and IRB review, regardless of funding source or sponsor.

SCOPE: This policy covers all research conducted within the purview of this IRB involving drugs, biologics, devices, diagnostics, and dietary supplements and food additives.

DEFINITIONS:

Expanded Access – “Compassionate Use”. Historically the terms “expanded access” or “compassionate use” have been used to describe a situation in which a patient is allowed to receive a test article even though he/she does not meet the eligibility criteria of a clinical trial in which it is being studied. It is the provision of a test article outside of an ongoing clinical trial to a limited number of subjects who are desperately ill and for whom no standard alternative therapies are available.

Emergency use means the use of a test article on 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.

Test articles means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

Investigational new drug (IND) means a new drug or biological drug used in a clinical investigation. The IND is an investigational new drug application and is synonymous with “Notice of Claimed Investigational Exemption for a New Drug.” An investigational drug must have an IND before it can be shipped.

Investigational device exemption (IDE) - An approved IDE permits a device not approved by the FDA to be shipped to conduct clinical investigations of that device. Not all investigational devices need an IDE.

Medical Devices. FDA device regulations differentiate between **significant risk (SR)** and **non-significant risk (NSR)** devices. A significant risk device must have an IDE issued by the FDA, while a non-significant risk device determination by an IRB grants the device an IDE. Thus, if a clinical investigation is submitted to the IRB for a device that has an IDE, the device is considered a SR device. A SR device (a) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject, or (b) is used in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject, or (c) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject or (d) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Adverse Event (AE) - is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Such events may be psychological, emotional, social, or physical and include any illness, sign, symptom, or clinically significant laboratory test abnormality that has appeared or worsened during the course of the experimental study regardless of causal relationship to the drugs and procedures under study. For observational studies (e.g., chart reviews, data base studies, surveys), deaths, life-threatening events or hospitalizations need not be reported as AEs. In addition, reports of subjects having complaints about the experimental procedures or about the conduct of the investigators may be reported as AEs. Serious AEs are defined in chapter 12.

Serious adverse drug experience is defined as "any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect".

Emergency use of a test article is defined as use of a test article on 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.

RESPONSIBILITIES:

IRB Chairperson – The Chairperson is responsible for protecting the health, safety, and welfare of human subjects participating in research studies involving test articles.

IRB Members – The members are responsible for reviewing and monitoring research activities involving test articles to ensure safety for the human subjects and compliance with FDA and other federal regulations.

Principal Investigator - The investigator is responsible for the conduct of the study and for leading the team of individuals coordinating the study. These responsibilities include obtaining IRB approval, obtaining informed consent from each subject, following the investigational plan, complying fully with the regulations, protecting the rights, welfare and safety of the subjects, supervising the use and

disposition of the test article, maintaining accurate, current, and complete records; and disclosing relevant financial information. FDA and DHHS regulations require the IRB to have policies and procedures to ensure **prompt** reporting to the IRB, FDA, OHRP of any unanticipated problems involving risks to human subjects and others. If the investigator provides an IND or IDE number then supporting documentation is required that verifies the number, such as a protocol from a sponsor, a letter from the sponsor, or letter from the FDA.

When Following VA Regulations - The PI is responsible for conducting VA human subjects research involving investigational drugs and devices in accordance with all applicable VA policies and other Federal requirements including, but not limited to, this directive; VHA Handbook 1108.04, Investigational Drugs and Supplies, dated February 29, 2012; and applicable FDA regulations. The storage and security procedures for test articles used in research must be reviewed and approved by the IRB and follow all applicable Federal laws, regulations, and VA policies.

Sponsor - The sponsor is responsible for initiating the clinical investigation, and holding the IND or IDE, but does not usually conduct the investigation. The sponsor is responsible for selecting qualified investigators, providing investigators with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, and ensuring that the FDA and (for devices) the IRB or (for drugs) all participating investigators are promptly informed of significant new information about an investigation. If MU (or an affiliate) or an individual wants to assume the sponsor function, then they should contact the Director, ORI to discuss the additional FDA regulatory requirements of sponsors to ensure that they will be followed. Below is a list of regulatory requirements:

- 1) Drugs or devices:
 - 1.1. 21 CFR §11 (Electronic records and electronic signature)
 - 1.2. 21 CFR §54 (Financial Disclosure by Clinical Investigators)
- 2) Drugs and Biologics:
 - 2.1. 21 CFR §210 (Current Good Manufacturing Practice In Manufacturing, Processing, Packing, Or Holding of Drugs; General)
 - 2.2. 21 CFR §211 (Current Good Manufacturing Practice for Finished Pharmaceuticals)
 - 2.3. 21 CFR §312 (Investigational New Drug Application)
 - 2.4. 21 CFR §314 (Drugs for Human Use)
 - 2.5. 21 CFR §320 (Bioavailability and Bioequivalence Requirements)
 - 2.6. 21 CFR §330 (Over-The-Counter (OTC) Human Drugs Which are Generally Recognized as Safe and Effective and Not Misbranded)
 - 2.7. 21 CFR §601 (Biologics Licensing)
- 3) Devices:
 - 3.1. 21 CFR §807 (Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices)
 - 3.2. 21 CFR §812 (Investigational Device Exemptions)
 - 3.3. 21 CFR §814 (Premarket Approval of Medical Devices)
 - 3.4. 21 CFR §820 (Quality System Regulation)
 - 3.5. 21 CFR §860 (Medical Device Classification Procedures)

IRB Coordinator - The IRB coordinator is responsible for maintaining documentation of emergency use of a test article and reporting the information at the next IRB meeting. The IRB coordinator will verify the IND or IDE number against the supporting documentation provided by the investigator. The IRB coordinator will also ensure that the protocols involving drugs include information allowing the IRB to determine whether FDA required and IND or IDE.

JURISDICTION:

When FDA regulated research is being done at Marshall University or funded by another federal agency, more than one set of regulations apply. For example, clinical trials involving FDA regulated test articles that are supported by DHHS (e.g., the National Institutes of Health) fall under the jurisdiction of both the FDA and the DHHS Office for Human Research Protections (OHRP). Such trials must comply with the FDA and the DHHS human subject regulations as well as the Common Rule. Where regulations differ, the IRB applies the more stringent.

The FDA regulations have important differences from the Common Rule requirements. These differences are:

- 1) FDA regulations contain no Assurance requirement.
- 2) Conditions for exemption, exception, and waiver of IRB review and informed consent requirements differ.
- 3) FDA regulations require specific determinations for the IRB review of device studies.
- 4) FDA regulations include specific requirements for reporting adverse events that are not found in the Common Rule, or DHHS regulations.

All research must comply with human subject regulations, as well as with all applicable regulations and requirements regarding storage, security, and dispensing procedures for investigational agents.

PROCEDURES:

If the investigator indicates that drugs are being used in the research and there is no IND, the IRB will use the worksheet “Criteria for Exemption from the Requirement for an IND.”

If the investigator indicates that devices are being used in the research to test their safety or efficacy and there is no FDA-issued IDE, the IRB uses the worksheet “Criteria for Exemption from the Requirement for an FDA-Issued IDE” to ensure that an FDA-issued IDE is not required.

When research involves the use of a drug other than the use of a marketed drug in the course of medical practice:

- 1) The drug has an IND; or

2) The protocol meets one of the FDA exemptions from the requirement to have an IND.

(a) Exemption 1

- i. The drug product is lawfully marketed in the United States.
- ii. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.
- iii. If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product.
- iv. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- v. The investigation is conducted in compliance with 21 CFR 50 and 56.
- vi. The investigation is conducted in compliance with the requirements of 21 CFR 312.7.

(b) Exemption 2

- i. A clinical investigation is for an in vitro diagnostic biological product that involves one or more of the following:
 - (1) Blood grouping serum.
 - (2) Reagent red blood cells.
 - (3) Anti-human globulin.
- ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.
- iii. The diagnostic test is shipped in compliance with 21 CFR 312.160.

(c) Exemption 4

- i. A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

The 30-day Rule for an IND Submission. After the FDA receives an application for an IND, an *IND Acknowledgement Letter* will be sent to the sponsor-investigator. The letter includes important information such as the assigned review division, IND number, division contact, and the official FDA date of receipt. The date of receipt is important because by regulation the proposed trial may not be initiated until 30 calendar days after official FDA receipt. The IRB can approve the trial during this 30-day period but will delay sending the approval letter until the IND goes into effect. By the end of this 30-day period, if the FDA makes the determination that it is safe to proceed with the clinical trial, the FDA may or may not contact the sponsor-investigator about its determination. Unless notified by the FDA within 30 days that a clinical hold has been placed, the trial can proceed as long as IRB approval has been obtained.

When research is conducted to determine the safety or effectiveness of a device:

- 1) The device has an IDE issued by the FDA.
- 2) The device fulfills the requirements for an abbreviated IDE:
 - (a) The device is not a banned device.
 - (b) The sponsor labels the device in accordance with 21 CFR 812.5.
 - (c) The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval.
 - (d) 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 is waived.
 - (e) The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations;
 - (f) 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);
 - (g) 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); and
 - (h) The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.
- 3) The device fulfills one of the IDE exemption categories:
 - (a) 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.
 - (b) 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 part 807 in determining substantial equivalence.

- (c) A diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
 - i. Is noninvasive.
 - ii. Does not require an invasive sampling procedure that presents significant risk.
 - iii. Does not by design or intention introduce energy into a participant.
 - iv. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- (d) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put participants at risk.
- (e) 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.

For an abbreviated IDE, the IRB must determine whether a device involves significant risk (SR) or non-significant risk (NSR) to subjects. The determination of the risk level is based on the proposed use of the device and not just the device itself. Clinical research involving an investigational device classified by the sponsor as NSR may be submitted to an IRB for review without an IDE. The sponsor/investigator must provide the IRB with a risk assessment and the rationale used in making its NSR risk determination. The IRB will review the information and make its own independent determination that the device is SR or NSR.

- 1) If the IRB disagrees with the sponsor's NSR determination, the IRB will notify both the investigator and the sponsor of its determination. The sponsor will need to submit an IDE application to the FDA. The study **will not** begin until the FDA approves the IDE **and the IRB approves the study**.
- 2) If the IRB determines that the device is classified as NSR, the clinical investigation may begin once IRB approval is obtained.
- 3) If FDA agrees that a new device is substantially equivalent to a device already on the market, it can be marketed without clinical testing. However, if clinical data are necessary to demonstrate equivalence, any clinical studies must be conducted in compliance with the requirements of the IDE regulations, IRB review, and informed consent.

The sponsor is required to obtain an IDE before the IRB will review a research protocol involving a significant risk device. Protocols involving significant risk devices do not qualify for an expedited review.

Radiology Devices and Radioactive Materials. FDA is responsible for regulating radiology devices and radioactive materials used in healthcare and research. Oversight at Marshall University is handled by the Radiation Safety Committee at each respective institution. Most clinical research being done

on FDA regulated test articles with either an IND or IDE will need initial review at a convened IRB meeting.

Adverse Event (AE) Notification – INDs. Refer to Chapter 12 of this SOP to obtain guidance on this issue.

Adverse Event Notification – IDEs. Refer to Chapter 12 of this SOP to obtain guidance on this issue.

Relationship of IRB to IND/IDE Sponsors. Unless specifically required by an IND or IDE sponsor or by FDA regulations, or by the IRB, no written notifications of IRB decisions will be provided by the IRB to the IND/IDE sponsors. For FDA regulated test articles clinical investigators, in complying with the requirements related to their obligations as investigators, serve as the link between IRB and sponsor. Investigators sign the FDA Form 1572, Statement of Investigator, which states their responsibilities.

“Off-label” (Unapproved) Use of FDA-Regulated Products in Medical Practice. FDA regulations allow that physicians may use approved drugs, devices, and biologics in the course of the practice of medicine in any manner they see fit.

“Off-label” (Unapproved) Use of FDA Regulated Products in Research. Such activities require IRB review and approval.

Expanded Access to Investigational Drugs - “Compassionate Use”. Investigational products are sometimes used for treatment of serious or life-threatening conditions either for a single subject or for a group of subjects. The procedures that have evolved for an investigational new drug (IND) used for these purposes reflect the recognition by the FDA that, when no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects or the thoroughness and scientific integrity of product development and marketing approval.

- 1) **Open Label Protocol or Open Protocol IND.** These are usually uncontrolled studies, carried out to obtain additional safety data. They are typically used when the controlled trial has ended and treatment is continued so that the subjects and the controls may continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective IRB review and informed consent.
- 2) **Treatment IND.** The treatment IND is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data has been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug. Four requirements must be satisfied before a treatment IND can be issued:

- (a) The drug must be intended to treat a serious or immediately life-threatening disease;
- (b) There must be no satisfactory alternative treatment available;
- (c) The drug must already be under investigation or the drug trials must have been completed; and
- (d) The trial sponsor must be actively pursuing marketing approval.

Treatment IND studies require prospective IRB review and informed consent.

- 3) **Parallel Track Studies.** FDA permits wider access to promising new drugs for HIV/AIDS related diseases under a “separate access” protocol that “parallels” the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. These “parallel track” studies require prospective IRB review and informed consent.

The FDA has three categories under the EAP based on the number of people who need access and the level of risk. An expanded access IND submission is required for each type of expanded access. The three categories are:

- 1) Individual patients, including for emergency use (21 CFR 312.310)
- 2) Intermediate-size patient populations (21 CFR 312.315)
- 3) Large patient populations treatment or treatment protocol (21 CFR 312.320)

The FDA does allow participants to be charged for the drug when used in an EAP if regulatory criteria are met (21 CFR 312.8(c)). Therefore, the IRB must pay particular attention to EAPs 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 may inadvertently be excluded from participation. Charging for participation may preclude economically disadvantaged persons as a class from receiving access to test articles.

The procedures for IRB approval of a drug for expanded access are as follows:

- 1) **Sponsor approval:** The investigator must obtain permission from the sponsor to use the drug outside of the clinical trial. The sponsor may refuse to allow the drug to be used based on limited availability or cost. If the sponsor agrees to allow the use of the drug for expanded access purposes then the investigator may proceed to the next step of obtaining FDA approval.
- 2) **FDA approval:** The investigator must obtain FDA approval under one of the three categories of the EAP. The FDA will grant the approval under the EAP if the investigator or physician can prove that the drug may be effective or does not have unreasonable risks comparable to the risk of the condition of treatment. If the FDA grants approval of the expanded access IND submission then the investigator may proceed to the next step of obtaining IRB approval.

- 3) **IRB approval:** The investigator must obtain IRB approval. The submission to the IRB must include the approval letters from the sponsor and FDA concerning the expanded use of the drug. The ORI staff will verify the IND number and all submissions must receive full board review.

Expanded Access to Investigational Devices – “Compassionate Use”. An unapproved medical device may normally only be used in human subjects when the device is under clinical investigation and when used by investigators participating in the clinical trial. However, a health care provider may wish to use an unapproved device to save the life of a subject, to prevent irreversible morbidity, or to help a subject suffering from a serious disease or condition for which there exists no alternative therapy. Four main mechanisms are utilized to make unapproved devices available to subjects/physicians faced with these circumstances. The sponsor must agree and FDA must approve the use. Under most circumstances such studies require IRB review and informed consent.

- 1) **Single Subject/Small Group Access to Investigational Devices.** Allows access to a device where the subject is not eligible for an ongoing clinical trial. The subject must have a serious condition/disease, with no alternative intervention available. Under some conditions, FDA may grant permission even if there is no pre-existing IDE.
- 2) **Treatment Use/IDE.** Allows wider access to a device during the clinical trial or prior to final action on marketing application. The subject must have a serious condition/disease, with no alternative intervention available.
- 3) **Continued Access to Investigational Devices.** Allows access to a device while a marketing application is being prepared and reviewed, and can be used to collect additional evidence of safety and effectiveness, as well as to address new questions regarding the investigational device, such as labeling claims. There must be a public health need for the device, as well as preliminary evidence that the device is effective.
- 4) **Access under a formal protocol.** Access in a controlled rate of enrollment and with no significant safety concerns identified for the proposed indication.

Note: The procedure for IRB submission is the same as the Expanded Access to Investigational Drugs.

Human Gene Transfer (HGT) Research. Gene transfer involves the administration of genetic material to alter the biological properties of living cells for therapeutic use. Gene transfer activities in humans are investigational and are regulated by the both the FDA and the National Institutes of Health (NIH) Office of Science Policy (OSP).

- 1) FDA regulations require the submission of an IND for human gene transfer research through the FDA Center for Biologics Evaluation and Research (CBER).

- 2) Department of Health and Human Services (DHHS) regulations specify that research cannot be initiated until Institutional Biosafety Committee and all other applicable institutional and regulatory authorization(s) and approvals have been obtained.

Emergency Use of a Test Article Without IRB Review. An exemption permits the emergency use of an investigational drug, device, or biologic on a one-time basis per institution without IRB review and approval. Any subsequent use of the investigational product at the institution will have prospective IRB review and approval. The following conditions **must** be met for this type of emergency use:

- 1) A human subject is in a life-threatening situation.
- 2) No alternate standard acceptable treatment is available.
- 3) There is insufficient time to obtain IRB approval.
- 4) The emergency use must be reported to the IRB within five working days. This reporting must not be construed as an approval for the emergency use by the IRB.
- 5) The investigator must obtain the informed consent of the subject for such an emergency use, except as described below:

The IRB#1 Chair verifies that conditions for the use meet the FDA regulatory requirements by evaluating the five-day report. If the IRB is notified of the use in advance, the IRB#1 Chair will also conduct a prospective evaluation of an investigator's intent to use a test article on an emergency basis in a life-threatening situation without prior IRB review to ensure that the conditions of the use will meet FDA regulatory requirements. Emergency use of a test article in a life threatening situation without prior IRB approval is research involving a human subject. However, the exemption does not apply if the use meets the DHHS definition of research involving human subjects. Such use may not be claimed as research as defined by DHHS regulations, nor may the outcome of such care be included in any prospective report of a research activity as defined in DHHS regulations.

A Sample Letter Template for Emergency Use Reporting is available on the ORI website.

Emergency Use of a Test Article Without Informed Consent. Regulations permit 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:

- 1) The subject is confronted by a life-threatening situation necessitating the use of the test article;
- 2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject;
- 3) Time is not sufficient to obtain consent from the subject's legally authorized representative;

- 4) 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 working days. The emergency use must be reported to the IRB within 5 working days. This reporting must not be construed as an approval for the emergency use by the IRB.

(Note: This use without prospective IRB approval is research involving a human subject. However, the exception for the requirement to obtain informed consent does not apply if the use meets the DHHS definition of research involving human subjects.)

The Director, ORI verifies that conditions for the emergency use have been met by evaluating the five-day report.

Humanitarian Use of a Device (HUD). A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. A device manufacturer's research and development costs could exceed its market returns for diseases or conditions affecting small patient populations. The HUD provision of the regulation provides an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations.

The following information is found in 21 CFR 814.124:

IRB approval. The HDE holder is responsible for ensuring that a HUD approved under this subpart is administered only in facilities having an Institutional Review Board (IRB) constituted and acting pursuant to 21 CFR 56, including continuing review of use of the device. In addition, a HUD may be administered only if such use has been approved by the IRB located at the facility or by a similarly constituted IRB that has agreed to oversee such use and to which the local IRB has deferred in a letter to the HDE holder, signed by the IRB chair or an authorized designee. If, however, a physician in an emergency situation determines that approval from an IRB cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior approval by the IRB located at the facility or by a similarly constituted IRB that has agreed to oversee such use. In such an emergency situation, the physician shall, within 5 days after the use of the device, provide written notification to the chairman of the IRB of such use. Such written notification shall include the identification of the patient involved, the date on which the device was used, and the reason for the use.

Initial IRB approval should be performed at a convened IRB meeting and continuing review of the HUD is required in accordance with IRB regulations 21 CFR Part 56. FDA allows continuing review to be conducted using the expedited review procedures (see 21 CFR 56.110) unless the IRB determines that full board review should be performed. Because a HUD is a legally marketed device, no systematic data is collected; however Medical Device Reporting (MDR) reports may provide risk and benefit information for continuing review.

Withdrawal of IRB approval. A holder of an approved HDE shall notify FDA of any withdrawal of approval for the use of a HUD by a reviewing IRB within 5 working days after being notified of the withdrawal of approval.

Managing Conflicts of Interest. The sponsor in a marketing application of any drug, device, or biologic must submit certain information on financial interests and arrangements of clinical investigators conducting studies to FDA. The following financial arrangements must be disclosed to the sponsor:

- 1) Any relationship between the study outcome and the value of the compensation made to the investigator.
- 2) The investigator's proprietary interest in the studied product, including but not limited to a patent, trademark, copyright or licensing agreement.
- 3) Any equity interest in the study sponsor, ownership interest, stock options, or other financial interest.
- 4) Any equity interest in a publicly held company that exceeds \$50,000 in value.
- 5) Significant payment of another type, which has a cumulative monetary value of \$25,000 or more, made by the sponsors to the investigator(s).

(See Chapter 8 of this SOP for information on the financial interests that investigators must disclose to the IRB.)

Pharmacy Policy. Where allowed or required, the investigator may assign some or all duties for investigational articles accountability at the trial sites to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator.

The investigator, pharmacist, or other designated individual will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused products. These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial participants. Investigators should maintain records that document adequately that the participants are provided the doses specified by the protocol and reconcile all investigational products received from the sponsor.

For **ICH-GCP** (E6) compliant studies the investigator must ensure the following:

- 1) Manufacturing, handling, and storage in accordance with applicable good manufacturing practice.

- 2) Where allowed or required, the investigator may assign some or all duties for investigational articles accountability at the trial sites to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator.
- 3) The investigator, pharmacist, or other designated individual will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused products. These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial participants.
- 4) Investigators should maintain records that document adequately that the participants are provided the doses specified by the protocol and reconcile all investigational products received from the sponsor.

Chapter 15 - Investigator Responsibilities for Submitting IRB Documents

PURPOSE: To establish guidelines for submitting the required documents to the Institutional Review Board (IRB) for research activities which involve human subjects.

POLICY: To delineate the specific protocol, informed consent, protocol application, assessment checklist, educational certificates, and other related documents that must be submitted to the IRB for review.

SCOPE: This policy covers all research activities that involve the IRB review process (e.g., full convened, expedited, continuing, training, protocol or informed consent changes, SAE/AEs, closures).

DEFINITIONS:

An **Investigator** is an individual who conducts a research study and under whose immediate direction the investigation is administered. When a team of individuals conducts an investigation, the responsibility leader of the team is the Principal Investigator (PI).

A **Protocol** is a document that states the background, rationale, and objectives of a clinical trial and describes in detail the design, methodology, and organization of a trial as well as the statistical methods and the situations likely encountered during the trial and their possible remedies.

RESPONSIBILITY:

The **Principal Investigator (PI)** is responsible for ensuring the well-being and safety of the study subjects. The PI must ensure the proper conduct of the study; adherence to the study protocol; and compliance with all applicable regulations, guidelines, and policies. The PI is responsible for submitting complete and accurate documents to the IRB in a timely manner.

Principal Investigators are responsible for the following:

- Acquiring the required training for PI and research staff before beginning any human subjects research.
- Requesting approval for planned research.
- Obtaining and documenting informed consent from all subjects.
- Requesting prior IRB approval for all changes in the research protocol or consent form.
- Notifying sponsoring agency of IRB actions.
- Submitting periodic reports to the IRB (*as required*).
- Promptly reporting serious adverse events, complications, and complaints. Also informing subjects of study related injuries.
- Notifying the IRB of study closure (*for Expedited and full board studies*).

- Permit FDA, Sponsor representatives, ORI/IRB representatives, and other Regulatory Officials to survey and inspect study records and information.
- Maintaining records.
- Keeping well informed about principles and procedures of human subjects protection.

ICH-GCP Specific Responsibilities for Investigators:

- During and following a participant's participation in a trial, the investigator ensures that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the clinical trial.
- The investigator informs a participant when medical care is needed for other illnesses of which the investigator becomes aware.
- The investigator follows the trial's randomization procedures, if any, and ensures that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator promptly documents and explains to the sponsor any premature unblinding.
- The investigator provides written reports to the sponsor and the IRB of any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.
- The investigator maintains a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.
- For reports deaths, the investigator supplies the sponsor and the IRB with any additional requested information (e.g. autopsy reports and terminal medical reports).
- The investigator must ensure that data reported on the Case Report Form (CRF) are consistent with source documents. Any change or correction on the CRF will be dated, initialed, and explained (if necessary) and will not obscure the original entry.
- The investigator must maintain the clinical trial documents that are not uploaded into IRBNet (i.e. signed consent forms) as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirements.

PROCEDURES:

Taking Required Training before beginning any human subject research. Each person engaged in human subject research has an obligation to acquire and apply an in-depth knowledge of the ethical principals (as in the Belmont Report) and good clinical practice that govern such research. Initial and continuing research ethics education is required for all personnel who conduct, review, approve, oversee, or manage human participant's research. To ensure that all personnel have a clear understanding of their responsibilities and obligations, the Marshall University Office of Research Integrity (ORI) has implemented an educational program. The educational requirements are included in the Protocol Application Form and can be found in chapter 11 of this SOP. There may be specific educational requirements or certification required for sponsored studies.

All individuals engaged in conducting research involving human subjects will be required to complete a training program. This includes all principal investigators, co-investigators, study coordinators, study nurses, and all individuals that will be listed on a Protocol Application Form. This training **MUST** be completed and the education module certificates submitted to ORI **BEFORE** any protocol may be submitted to the IRB for review and approval.

Requesting Approval For Planned Research. A principal investigator planning a new research project must complete and submit the following documents for IRB review and approval. These documents must be submitted on IRBNet no later than 30 Days in advance of the date of the meeting in which they desire the protocol reviewed (if it is a full board study):

- Completed Protocol Application (Must include CVs, Current License and Board Certification information of PI, Co-PI and all Research Staff, Training documentation of all research personnel, and completed Attachment C forms for all staff).
- Copy of Protocol and all associated documents relevant to the study. (this includes the abstract, and any survey instrument or interview guide)
- Informed Consent, Assent, or Requests for Waivers
- Applicable Protocol Assessment Form
- Any relevant grant applications or sponsor contracts.
- 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)

Detailed instructions for a protocol submission are provided in the IRBNet library or on the ORI website at www.marshall.edu/research/ori or if you have additional questions, please contact the Office of Research Integrity (ORI) at (304) 696-4303.

NO HUMAN SUBJECTS MAY BE INVOLVED IN ANY RESEARCH PROJECT UNTIL IT HAS BEEN REVIEWED AND FULLY APPROVED BY THE IRB!

Obtaining And Documenting Informed Consent From All Subjects. It is unethical to conduct research without freely given consent or to take advantage of a subject's situation as a patient or client to induce participation in research without consent on the basis of complete information. The process of Informed Consent involves several essential features that are described in detail in chapter 13 of this SOP. The IRB must approve all consent forms that will be used for enrolling research subjects. The consent form will contain a stamp that indicates the approval and expiration date (if applicable). If your study does not require the use of consent, a request for Waiver of Informed Consent must be submitted for approval unless you are applying for Exempt status. A template of the consent waiver is available in the IRBNet library.

Requesting PRIOR IRB approval for all changes in the research protocol or consent form. All desired or contemplated changes in the research protocol or the consent form must be submitted to the IRB for review and approval. This may include any changes or new information that may affect the risk/benefit assessment of the study or any significant new findings that may affect, or relate to a subject's willingness to continue their participation in the research.

Notifying sponsoring agency of IRB actions. It is the responsibility of the Principal Investigator to notify the Research Sponsor of all IRB actions.

Submitting Annual Updates and Continuing Reviews.

- 1) Expedited protocols will not require a continuing review, however the following completed documents must be submitted to the appropriate board for administrative review via IRBNet on an annual basis:
 - (a) Annual Update Form.
 - (b) Current CITI educational certificates for all members of the research study.
 - (c) Any additional items that the investigator may request to be amended into the study.

Note: Failure to submit an annual update will result in suspension/termination of the study.

- 2) Full Board studies must receive annual review unless otherwise stated or the study is granted Expedited continuing reviews by the convened board. The IRB makes the determination of the frequency for continuing review for each full board protocol after the initial approval but that approval is not to exceed 1 year. It is the responsibility of the Principal Investigator to comply with the continuing review requirements and must submit the required documentation in a timely manner in order to insure that there will be no interruption in the research process. The Principal Investigator must ensure that their protocol does not exceed the expiration date that has been initially approved. The following completed documents must be submitted to the appropriate board via IRBNet at least 30 days in advance of the next IRB meeting date that does not exceed the expiration of the protocol:
 - (a) Continuing Review Protocol Assessment Form.
 - (b) Continuing Review Request Form.
 - (c) A Copy of the consent form so a new stamp can be inserted.
 - (d) Current CITI educational certificates for all members of the research study.
 - (e) Any additional items that the investigator may request to be amended into the study.

In the event that the full board protocol does not receive continuing review by the required date, the study will be closed and must be submitted as a new protocol. Every effort will be made by the ORI/IRB Office to ensure that the Principal Investigator is aware of the expiration date ahead of time, but the Principal Investigator has the responsibility for the timely submission of their protocol information. IRBNet will send out expiration reminders at 60/30/14/7 day intervals. All Continuing Review documents may be found in the IRBNet forms and templates library. If you have additional questions, please contact the Office of Research Integrity (ORI) at (304) 696-4303. *(In the event that a study will be ending or closed just before the continuing review date, please submit the closure package on IRBNet.)*

Promptly Reporting Serious Adverse Events, Adverse Events, Complications, and Complaints.

Principal Investigators must promptly report serious adverse events, adverse events, complications, and complaints to the IRB to ensure the protection of research subjects and to comply with federal and other regulations.

- 1) **Serious Adverse Events, Adverse Events, and Complications:** For information on the reporting of all AEs and SAEs refer to chapter 12 of this SOP and other information located on the ORI/IRB website.
- 2) **Complaints:** All complaints received from study subjects to the Principal Investigator must be submitted to the ORI/IRB Office. Please refer to chapter 6 of this SOP and other information located on the ORI/IRB website.

Notifying The IRB Of Study Closure. The Principal Investigator must notify the IRB through an IRBNet submission of study closure for Expedited and full board studies before a study can be formally closed. As part of the request for closure, the PI should include a final report, which should include any findings as a result of the study. There is a Closure Request Form located in the Forms and Templates Library on IRBNet. The study will be closed by the IRB coordinator and documented in the agenda of the next IRB meeting.

Permit FDA, Sponsor representatives, ORI/IRB representatives, accreditation body, and other Regulatory Officials to survey and inspect study records and information. Periodically, there will be a requirement to review IRB approved research study information. The Principal Investigator must comply and cooperate with request for an audit from any of regulatory officials listed previously. There are different types of audits that may take place such as: Subject surveys, consent process observation, random protocol file audits, random subject study file audits, research data review, interviews with PIs, Co-PI, and research staff, and many other methods may be introduced. These audits are very important and must be conducted to ensure the safety of human subjects is maintained at all times.

Maintaining Records. The Principal Investigator must protect and maintain all research-related documentation in a secure location as indicated on the initial protocol application. The PI must maintain adequate and accurate documentation of case histories for each subject that records all observations and data gathered during the study subject's participation and research visits. In addition, the investigator must maintain accurate and complete records of the receipt, dispensing, and return of all clinical supplies including study drugs. All such discrepancies must be noted and explained. All study documentation must be maintained and secured for 3 years after final closure of the study. Please note that study sponsors may have additional requirements for maintaining study documentation. Study Sponsor requirements must be acknowledged in addition to the ORI/IRB regulations.

Keeping Well Informed About Principles and Procedures of Human Subjects Protection. It is the responsibility of the Principal Investigator to keep up-to-date on new information and regulations concerning the protection of human subjects involved in research. The ORI/IRB website will be maintained with the most up-to-date information involving research. All Standard Operating

Procedures will be continuously updated to reflect new regulations as they are released. The PI must make every effort to read this SOP and any other information that is available concerning human research. The PI must comply with educational training requirements and can inquire about additional training that is available with the ORI/IRB Office.

Radiation and BioSafety Concerns. It is the responsibility of the principal investigator to ensure that radiation and biosafety issues have been reviewed and approved by the respective committee. The radiation and biosafety committees from the respective institution are responsible for that review.

- 1) Radiation - If a study involves any **additional** radiation procedures (i.e. x-rays) then documentation must be submitted from the Radiation Safety Committee of the respective institution to indicate approval for those procedures.
- 2) BioSafety – If a study involves biosafety issues (i.e. recombinant DNA or viral vectors) then documentation must be submitted from the BioSafety Committee (or equivalent) of the respective institution to indicate approval for those procedures.

The IRB member(s) reviewing a study must be aware of these issues and ensure that proper committee review and approval has been granted prior to IRB approval.

When Following DoJ Regulations:

- For research conducted within the Bureau of Prisons, the investigator must have academic preparation or experience in the area of study of the proposed research.
- For research conducted within the Bureau of Prisons, the investigator must assume responsibility for actions of any person engaged to participate in the research project as an associate, assistant, or subcontractor to the investigator.
- For research conducted within the Bureau of Prisons, when submitting a research proposal, the applicant shall provide the following information:
 - A comprehensive statement, which includes:
 - Review of related literature.
 - Detailed description of the research method.
 - Significance of anticipated results and their contribution to the advancement of knowledge.
 - Specific resources required from the Bureau of Prisons.
 - Description of all possible risks, discomforts, and benefits to individual subjects or a class of subjects, and a discussion of the likelihood that the risks and discomforts will actually occur.
 - Description of steps taken to minimize any risks.
 - Description of physical or administrative procedures to be followed to:
 - Ensure the security of any individually identifiable data that are being collected for the study.
 - Destroy research records or remove individual identifiers from those records when the research has been completed.

- Description of any anticipated effects of the research study on organizational programs and operations.
- Relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules.
- A statement regarding assurances and certification required by 28 CFR 46, if applicable.

Chapter 16 - IRB Documentation and Record Retention

PURPOSE: To establish guidelines for documentation of the activities of the IRB to assure compliance with 38 CFR 16, Food and Drug Administration (FDA) regulations, and other federal regulations.

POLICY: It is the policy to maintain a system of records that accurately records the activities of the Institutional Review Board.

PROCEDURES:

Access to and Record Retention. The IRB records are retained for at least 3 years after the completion of the research, and all other records are retained for at least 3 years. Records for VAMC research are retained after the completion of the study and are maintained in accordance with VA Records Control Schedule (RCS 10-1). Records for studies canceled without participant enrollment must be maintained for the above period of time after cancellation. Marshall University personnel are bound by all legal and ethical requirements to protect the rights of research subjects, including the confidentiality of information that can be identified with a person. All IRB records are maintained on IRBNet and any additional files are kept secure in locked file cabinets in the Office of Research Integrity or other secured areas. This program (IRBNet) is compliant with 21CFR11 and electronic signatures are in accordance with Subpart C of that instruction. Access to IRB records for inspection or copying is limited to the Director, ORI, the IRB Chairperson, IRB members, IRB Coordinator, ORI staff, authorized MU representatives, accreditation organizations contracted by ORI, and officials of Federal and state regulatory agencies, including the Office for Human Research Protections (OHRP), and the Food and Drug Administration (FDA). Research investigators are provided reasonable access to files related to their research. All other access to IRB records for inspection or copying is limited to those who have legitimate need for them, as determined by the Director, ORI. For VAMC research, the VA Research and Development Committee has access to IRB records. Department of Defense-sponsored research may require submitting records to Department of Defense for archiving.

IRB Records. The following is a list of some of the IRB records:

- Written operating procedures
- IRB membership rosters
- All IRB correspondence
- IRB research application (protocol) files
- Research (protocol) tracking system
- Documentation of exemptions and exceptions reviews
- Documentation of expedited reviews
- Documentation of convened IRB meetings (i.e., IRB minutes)
- Documentation of review by outside consultants when appropriate
- Federal Wide Assurances (FWA)

- Serious Adverse Event (SAE) reports
- Project tracking documents from automated system
- Documentation of cooperative review agreements, e.g., Memorandum of Agreements (MOAs)
- DHHS-approved sample consent documents
- Progress reports submitted by investigators
- Reports of injuries to participants
- Records of continuing review activities
- Statements of significant new findings provided to participants
- Correspondence between the IRB and the Research and Development Committee
- Protocol violations submitted to the IRB
- A resume for each IRB member
- Unexpected adverse events submitted to the IRB

IRB records will document determinations required by the regulations and protocol-specific findings supporting those determinations. IRB records for each study's initial and continuing review will note the frequency for the next continuing review.

IRB Membership Rosters. The Director, ORI ensures that current IRB membership rosters are maintained to detail the membership of the IRB. The membership rosters include the following information:

- Names of IRB members.
- Names of alternate members (if any) and the corresponding regular member(s) for who each alternate may serve.
- Earned degrees of each member and alternate, where applicable.
- Specific scientific qualifications (such as board certifications and licenses) or other relevant experience sufficient to describe each member's chief anticipated contribution to IRB deliberations.
- The representative capacity of each member or alternate.
- Any employment or other relationship with Marshall University or with the collaborating institutions (e.g., full or part time employee, stockholder, member of governing board, paid or unpaid consultant).
- Scientific/Nonscientific status.
- Affiliation status (whether the member or an immediate family member of the member is affiliated with the organization).
- For IRB#1 – Annotation that the member has been appointed as a VA representative by the VA Medical Center Director in the past three years.

Education and Training Records. All IRB members, research investigators, and other staff must complete the required orientation and training as outlined in Chapter 11 Education and Training. Documentation of completion of the mandated education is to be submitted as part of the required documents for a complete submission.

IRB Correspondence. All research investigators and staff involved with human subject research must provide the IRB with copies of any reports or correspondence concerning research in which they

are involved to or from any regulatory or compliance enforcement Federal agency, such as OHRP, or the FDA that exercises oversight over the protection of human subjects in research. Copies of all reports or correspondence to or from various government agencies concerning the facility's research is provided to the IRB which determines whether any additional notifications are necessary. The IRB Coordinator ensures that accurate records are maintained of all such correspondence.

IRB Research (Protocol) Application Files. The IRB maintains a separate file for each research application (protocol) that it receives for review on IRBNet. Protocols are numbered by the IRBNet system, in the order in which they are initially received. Each IRB research application (protocol) file contains the following materials (if applicable):

- The IRB Research (Protocol) Application Form. (Include waivers, if any)
- The IRB-approved informed consent document, with the approval date. (Note: Any change to the consent form will require an amendment to the study. All previously approved consent forms are retained in IRBNet.)
- Scientific evaluations of the proposed research, if any. For drugs, the Investigator's Brochure; for devices, a report of prior investigations.
- Applications for Federal support, if any.
- A complete copy of the protocol, or research plan, or investigational plan (projects which receive no direct funding, sponsor or cooperative group protocols).
- An abstract consisting of no more than 2 pages and written in lay terms.
- Advertising or recruiting materials, if any.
- Protocol amendments or modifications.
- Continuing review progress reports and related information.
- Reports of unanticipated problems involving risks to subjects or others.
- Reports of adverse events occurring within the Institution (or involving employees or agents of the Institution) and reported to any regulatory agency.
- Reports of external adverse events received from sponsors or cooperative groups.
- Data and Safety Monitoring Board (DSMB) reports, if any.
- Results of any internal quality control and monitoring activities.
- Results of any external monitoring activities, including reviews provided to the investigator by sponsors, cooperative groups, or Federal agencies.
- All IRB correspondence to or from research investigators.
- All other IRB correspondence related to the research.
- Documentation of all IRB review and approval actions, including initial and continuing convened (full) IRB review.
- Documentation of project closeout.
- Documentation of non-compliance.

Research (Protocol) Submission System. The IRBNet online submission system is utilized to submit, maintain and track all protocols presented to the IRB. Funding for protocols is tracked through the Marshall University Research Corporation (MURC). Some of the IRBNet fields we can track are:

- Title of the Research (Protocol)

- Names of principal investigator and co-investigators where appropriate
- Date of initial approval
- Date of most recent continuing approval
- End of current approval period
- Type of review (expedited, convened review, or exempt)
- Current status (pending review, approved, modifications required, suspended, closed)

Note: You can contact the Director, ORI to obtain various spreadsheet reports from the IRBNet system.

Documentation of Convened IRB Meetings in the Minutes. The IRB Coordinator compiles the minutes of IRB meetings. The minutes of the IRB proceedings must be written and available for review within 3 weeks of the meeting date. The following specific information is recorded in the meeting minutes:

- 1) **Attendance at IRB Meetings.** The IRB minutes list attendance as follows:
 - (a) Names of members present.
 - (b) Names of alternates (if applicable) attending in lieu of specified (named) absent members. Alternates may substitute for specific absent members only as designated on the official IRB membership roster.
 - (c) Names of consultants present.
 - (d) Names of investigators present.
 - (e) Names of guests present.

Each vote will reflect the number of voting "Members Present" at the meeting. Each vote will also list the number of votes "For", "Opposed" and "Abstained". Any member recused for that vote will be also be listed by name. A copy of the IRB roster is attached to every meeting agenda on IRBNet to show the full IRB membership for that meeting date.

- 2) **Quorum Requirements and Voting at IRB Meetings.** The IRB Coordinator is responsible to monitor the members present at convened meetings and determine that meetings are appropriately convened and remain so. A quorum requires that more than 50% of the IRB members listed on the official roster are present (including via telephone).

Quorum Requirements:

- (a) A majority of the IRB members (or their designated alternates), including at least one member whose primary concerns are in nonscientific areas **must** be present to conduct a convened meeting. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting. An unaffiliated member is

required to be present at least 10 out of 12 annual meetings. The Director, ORI will verify, on the annual HRPP report, that this requirement has been met.

- (b) Members may be present in person or audio (telephone) or audio-visual teleconference. Members present via teleconference are noted as such in the meeting minutes, which also indicate that the members received all pertinent information prior to the meeting and were able to actively and equally participate in all discussions.
- (c) IRB minutes include documentation of quorum and votes for each IRB action and determination by recording votes as follows: Total Number Voting (); Number voting For (); Number voting Opposed (); Number Abstained () and Name of any Recused.
- (d) Members recusing themselves due to conflicts of interest may not be counted toward quorum requirements (i.e., may not be counted among those voting or abstaining) or be counted as among the majority of members necessary to constitute a quorum.
- (e) An individual who is not listed on the official IRB membership roster may not vote with the IRB. Proxy votes are not allowed.
- (f) Any ex-officio member of the IRB may not vote with the IRB.
- (g) Ad hoc consultants may not vote with the IRB.
- (h) A non-scientific member **must** always be present for a vote to be taken. The non-scientific member can also be a member who is not otherwise affiliated with the institution and is not part of the immediate family of a person who is affiliated with the institution. In other words, the non-scientific member can also be counted as a non-affiliated member if he/she meets those qualifications.
- (i) If research involving a FDA regulated article is involved, a licensed physician must be included in the quorum. If a quorum is not maintained, the proposal must be tabled or the meeting must be terminated.
- (j) For research involving prisoners, a majority of the IRB (exclusive of prisoner members) must have no association with the prison involved. At least one member of the board present at the meeting will be a prisoner representative.

Should the quorum fail during the meeting (e.g., loss of a majority through recusal of members with conflicting interests or early departures, or absence of a nonscientist member), the IRB may **not** take further actions or votes unless the quorum can be restored.

- 3) **Actions Taken by the Convened IRB.** The IRB minutes include all actions taken by the convened IRB and the votes underlying those actions. These actions are also provided in writing to investigators after formal approval from the IRB is received. The IRB actions for initial or continuing review of research include the following:

- (a) Approved with no changes (or no additional changes). The research may proceed.
 - (b) Modifications Required. Revisions to be reviewed by the IRB Chairperson or a designated IRB member. Such minor revisions must be clearly delineated by the IRB so the investigator may simply concur with the IRB's stipulations. These revisions should not include the use of words like "clarify", "explain" or "provide more information" since they are not specific and would require a judgment that the full board should make. The research may proceed **after** the required changes are verified and the protocol approved by the designated reviewer.
 - (c) Modifications Required. Revisions to be reviewed at a convened IRB meeting. The research may proceed only after the convened IRB has reviewed and approved the required changes to the research.
 - (d) Deferred pending receipt of additional substantive information. The IRB determines that it lacks sufficient information about the research to proceed with its review. The research may not proceed until the convened IRB has approved a revised application incorporating all necessary information.
 - (e) Not Approved. The IRB has determined that the research cannot be conducted at the facility or by employees or agents of the facility.
- 4) **Votes**. The voting on any actions at the IRB meetings are categorized by "for, opposed, abstained, or recused due to a conflicting interest".
 - 5) **Changes in research activity**. The minutes of IRB meetings include the basis for requiring changes in or disapproving research (including statements of significant new findings).
 - 6) **Controverted issues**. The minutes include a written summary of IRB findings, determinations, and discussion of all controverted issues and their resolution.
 - 7) **IRB Findings and Determinations**. The IRB findings and determinations are provided in writing to the investigator, who is given an opportunity to respond in person or in writing. Certain findings may be documented in other formats, such as reviewer checklists that are filed in the protocol files. The following findings and determinations will be documented in the IRB minutes or on approved checklists:
 - (a) The level of risk of the research.
 - (b) The approval period for the research, including identification of research that warrants review more often than annually.

- (c) 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, if the IRB deems it necessary. (e.g., Cooperative Studies, or other collaborative research).
- (d) Justification for waiver of the requirement for written documentation of consent in accordance with the criteria at 38 CFR 16.117(c).
- (e) For DHHS-supported research, justification for approval of research involving pregnant women, human fetuses, and neonates involved in research, addressing each of the criteria specified under 45 CFR 46 Subpart B of the DHHS human subject regulations. (See Chapter 25 Vulnerable Subjects)
- (f) For DHHS-supported research, justification for approval of research involving prisoners, addressing each of the categories and criteria specified under 45 CFR 46 Subpart C of the DHHS human subject regulations. The IRB Coordinator is responsible for providing certification of the IRB's findings to OHRP.
- (g) For DHHS and FDA regulated research, justification for approval of research involving children, addressing each of the categories and criteria specified under 45 CFR 46 Subpart D of the DHHS and FDA human subject regulations. The IRB Coordinator is responsible for providing notification to OHRP of the IRB's findings concerning research requiring review by a panel of experts convened in accordance with Subpart D. For FDA regulated research, documentation of the IRB findings is required and notification goes to the Commissioner of the FDA.
- (h) Special protections warranted in specific research projects for groups of subjects who 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, regardless of source of support for the research.
- (i) Justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample informed consent document.
- (j) The rationale for significant risk/non-significant risk device determinations.
- (k) Information provided by consultants who attend IRB meetings to provide additional expertise to the IRB.
- (l) When an alternate member replaces a primary member.
- (m) Provide a summary of the discussion when real Social Security Numbers (SSNs), scrambled SSNs, or the last four digits of SSNs will be used in the study. The summary needs to include the security measures that are in place to protect the SSN instances embedded in the study. **(NOTE: This does not apply if the only use of SSNs is on the**

informed consent form or the HIPAA authorization as required by VHA Handbook 1907.01.)

A copy of the minutes will be made available to the following:

- MU Institutional Official
- Director, Office of Research Integrity
- HRPP representative of each affiliated institution
- VA Research and Development Committee

Research contingent on specific minor conditions by the chair or designee will be documented in the minutes of the first IRB meeting that takes place after the date of the approval. The minutes will be written and available for review within three weeks of the meeting date. Once approved by the members at a subsequent IRB meeting, the minutes may not be altered by anyone including a higher authority.

Members that recuse themselves. Members who recuse themselves will be listed by name in the voting section of that study and will appear in the IRB minutes.

OTHER DOCUMENTATION REQUIREMENTS:

Documentation of Expedited Reviews. Expedited IRB review procedures are employed only for (1) minor changes in previously convened approved research during the specified approval period, or (2) initial review of research falling within specific categories. Expedited reviews are conducted by the IRB Chairperson or a qualified IRB member designated by the Chairperson. Documentation for expedited review and approval consists of the reviewer's concurrence with the Expedited Checklist found in the IRB research application file that the research activity described in the investigator's Application for Expedited Review satisfies the conditions (1) for a minor change, or (2) involves minimal risk. Investigators must report to the IRB any proposed changes in previously approved IRB research, including proposed changes in informed consent documents. No changes may be initiated without prior approval of the IRB, except where necessary to eliminate apparent immediate hazards to subjects. The investigator will be notified in writing of the final decision.

IRB records for initial review by the expedited procedure will include:

- The specific permissible category
- Description of action taken by the reviewer
- Any findings required under the regulations

Procedure for Documentation of Exemptions. The investigator completes the IRB Initial Protocol Application, which includes a checkbox to request exempt status. The IRB Exempt Reviewer, IRB Chairperson or his/her designee reviews the protocol for exempt status based on the exempt categories. The investigator indicates on the Exempt Checklist under which category he/she believes is appropriate and reviewer will determine if the protocol meets that exempt status. If the protocol meets exempt status, the IRB Coordinator will report that decision to the IRB as informational. The investigator is notified in writing of the final decision. Categories of exempt research are listed in

Chapter 24 Types of Research and Types of Reviews. The IRB records for exempt determinations will include the specific category of exemption determined by the reviewer.

Documentation of Exemptions from IRB Review Requirements for Emergency Use of a Test

Article. Emergency use of a test article without IRB review is permitted. Emergency use is defined as use of a test article on 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. Written documentation of the emergency use must be submitted to the IRB within 5 working days. Any subsequent use of the test article requires IRB review. The IRB Coordinator is responsible for maintaining this documentation in the IRB records.

Documentation of Exceptions from Informed Consent Requirements for Emergency Use of a

Test Article. It is permitted to use a test article without the informed consent of the subject (or the subject's legally authorized representative) where the clinical investigator and a physician not otherwise involved in the research certify in writing that:

- the subject is confronted with an immediately life threatening emergency;
- informed consent cannot be obtained because of an inability to communicate;
- time is not sufficient to obtain consent from the subject's legally authorized representative; **and**
- there is no alternative approved or generally recognized therapy that provides equal or greater likelihood of saving the subject. If time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by an independent physician.

This written certification **must** be submitted to the IRB **within 5 working days** of the use of the test article. The IRB Coordinator is responsible for maintaining this documentation in the IRB records. The IRB Chairperson and the Director, ORI must verify that conditions for the use have been met.

When Following DHHS Regulations:

- Records must include the rationale for conducting continuing review on research that otherwise would not require continuing review.
- Records must include the rationale for an expedited reviewer's determination that research appearing on the expedited review list is more than minimal risk.
- Records must include documentation specifying the responsibilities that a relying organization and an organization operating an IRB each will undertake to ensure compliance with the requirements of the Common Rule.

When Following DoD Requirements:

- Records are maintained that document compliance or non-compliance with DoD requirements shall be made accessible for inspection and copying by representatives of the DoD at reasonable times and in a reasonable manner as determined by the supporting DoD component.

Chapter 17 - IRB Membership

PURPOSE: To establish guidelines for the IRB members, the IRB Chairperson, and other officials, to delineate the principles, authority, and the responsibilities of the IRB. The IRB's primary responsibility is to ensure that the rights, safety, and welfare of human subjects are protected under the facility's Human Research Protection Program (HRPP). The IRB ensures that human subject research is conducted ethically, and in compliance with Federal regulations, the requirements of state law, the institution's policies, and the Federal Wide Assurance (FWA). The IRB accomplishes prospective and continuing review of this facility's human subject research and this includes the review of protocols, informed consent process, and procedures used to enroll subjects.

POLICY: To appoint the Chairperson and members in compliance with all applicable federal regulations and to ensure the members are cognizant of the rules and responsibilities for which they must abide.

SCOPE: The IRB must prospectively review and make decisions concerning all human subject research conducted under the auspices of Marshall University or other institutions that have entered into a Memorandum of Agreement (MOA) with MU for their IRB reviews. The Board has statutory authority to take any action necessary to protect the rights and welfare of human subjects. The IRB has the authority to approve, require modifications in, or disapprove the facility's human subject research.

PRINCIPLES: The basic ethical principles guiding research involving human subjects are provided in the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report. Three basic principles contained in The Belmont Report are central to the ethics of research involving human research and guide the IRB in assuring that the rights and welfare of subjects are protected.

These principles are:

- **Respect for persons**, which is applied by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.
- **Beneficence**, which is applied so that possible benefits are maximized and possible risks are minimized to the persons, involved.
- **Justice**, which is evidenced in the equitable selection of subjects.

DEFINITIONS:

Human Subject Research – This topic is defined in Chapter 1 Introduction.

Research – This topic is defined in Chapter 1 Introduction.

Human subject - This topic is defined in Chapter 1 Introduction.

Physician is defined, in this document, as anyone with a doctorate-level health science degree (M.D., D.O., O.D., DMD, DPM, etc.).

Private information - information about behavior that occurs in a context 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 means that the identity of the individual is or may readily be ascertained by the investigator or associated with the information.

Community Representative - a 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.

If the activity involves a drug other than the use of an approved drug in the course of medical practice, the evaluation of the safety or efficacy of a medical device, or data that will be submitted to or held for inspection by FDA and the activity involves a human subject as defined by FDA regulations, the FDA regulations apply.

The definition of human subject includes investigators, technicians, and other assisting investigators when they serve in “subject” roles by being observed, manipulated, or sampled.

RESPONSIBILITIES:

The ethical conduct of research is a shared responsibility among the Institutional Official, IRB Chairperson, IRB members, the research investigators, and their staff.

Institutional Official (Assurance Signatory Official) – As the Institutional Official, the Vice President for Research ultimately is responsible for overseeing the protection of human subjects. He/she must ensure that open channels of communication are maintained between the IRB, research investigators, staff, and management. The Director of the Office of Research Integrity serves as the conduit between the VP for Research and the IRB. He/she meets at least quarterly, and whenever necessary, to assure the Institutional Official is kept abreast of all issues involving human subjects. The VP for Research has an open-door policy that allows any IRB member, investigator or staff to contact him. He/she is responsible for assuring resources are allocated appropriately and is responsible for completing the necessary educational requirements.

Director of the Office of Research Integrity – The Director, Office of Research Integrity, is responsible for assuring the policies and procedures are accurate and are in compliance with the federal guidelines. He/she serves as a non-voting member of the IRB and facilitates communication between the IRB members, investigators and the VP for Research. The Director meets with the Institutional Official at least quarterly to report on the activities of the ORI. Annually, he/she submits a report to the IO detailing the current human, financial, and physical resources utilization and any future resource requirements. The Director is responsible for completing the necessary educational requirements. The Director is responsible for the selection and appointment of IRB Chairs and conducting annual performance reviews. He/she will also select members of the IRB for annual interviews. This member selection should include representation of scientific, non-scientific and

community members. The Director is responsible to determine if a newly appointed IRB member is affiliated with the organization or has an immediate family member that is affiliated.

IRB Chairperson - In addition to the responsibilities as a member, the Chairperson has primary responsibility for conducting IRB meetings and assuring the IRB operates within all applicable regulatory requirements. The IRB Chairperson works with the IRB members, institutional officials, and investigators to ensure that the rights and welfare of research subjects are adequately protected. As a fair and impartial committee head, the Chairperson functions as a role model for how IRB business should be conducted. He/she schedules and conducts the IRB meetings in accordance with Robert's Rules. He/she assures that all IRB minutes are recorded accurately and are kept in accordance with federal policy. The IRB Chairperson assures that members having a conflict of interest on research activities are not allowed to be present to vote on the research activity. He/she is responsible for assuring a quorum is maintained when voting. He/she is responsible for completing the necessary educational requirements. The IRB Chairperson is protected from liability under the State of West Virginia's general liability insurance pursuant to Article VI Section 35 of the WV Constitution. Since service on the IRB requires a significant amount of time, the Chairperson has time allotted for his IRB responsibilities. The IRB Chairperson must make the ORI Director aware of any immediate family members who are currently or become affiliated with the organization. The Director, ORI will conduct an annual evaluation of the performance of IRB chairs.

IRB Members – Members and alternate members are responsible for reviewing and monitoring research involving human subjects and to protect the rights and welfare of subjects. Members are expected to attend IRB meetings on a regular basis and alternate members are expected to attend IRB meetings when possible or as needed. Members and alternate members serve as primary or secondary reviewers as assigned by the Chairperson for research within their areas of expertise, and serve as general reviewers on all research discussed at convened meetings. Members and alternate members are also expected to conduct expedited reviews on behalf of the IRB when so designated by the IRB Chairperson. In addition, the members may be asked to serve as designee to the Chairperson and to participate in other subcommittees, audits, and education, as long as there is no conflict of interest with their IRB responsibilities. The IRB members and alternates are responsible for completing the necessary educational requirements. IRB members and alternates must make the ORI Director aware of any immediate family members who are currently or become affiliated with the organization. The IRB members and alternates are protected from liability under the State of West Virginia's general liability insurance pursuant to Article VI Section 35 of the WV Constitution. Since service on the IRB may require a significant amount of time, the supervisors of the members and alternate members have agreed to allow them adequate time to fulfill their IRB responsibilities. The Director, ORI is responsible for the selection and appointment of members and alternate members and will conduct an annual evaluation of the performance of IRB members/alternates. These evaluations will be conducted in September of each year and documented with a copy placed in each IRB member's folder.

Ex-officio member – The IRB Coordinator serves as an ex-officio (non-voting) member and is responsible for distributing the agenda and research activity documents, taking minutes, maintaining the roster and quorum requirements, and that minutes are distributed, as appropriate, as well as all other duties detailed in other IRB related standard operating procedures. The IRB Coordinator assigns

the primary and secondary reviewers to appropriately knowledgeable IRB members or consultants, when necessary.

AUTHORITY and RELATIONSHIPS:

Authority - The Institutional Official is responsible for all research activities conducted under the auspices of Marshall University. The IRB prospectively reviews and makes a decision concerning all human subject research conducted under the auspices of Marshall University or other institutions that have entered into a Memorandum of Agreement (MOA) with MU for their IRB reviews. The IRB has statutory authority to take any action necessary to protect the rights and welfare of human subjects in the VA facility's research program. The IRB also has the authority to approve, require modifications in, or disapprove the facility's human subject research and to conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. The IRB has authority to suspend or terminate the enrollment or ongoing involvement of human subjects in research as it determines necessary for the protection of those subjects. The IRB has the authority to observe or monitor the human subject research to whatever extent it considers necessary to protect the subjects.

Relationships: Although the IRB is a Board administered through the Office of Research Integrity, neither the Director of ORI nor the VP for Research or other University official can approve research involving human subjects that has not been approved by the IRB. If in the course of its review, a University department requires changes to the protocol that may relate to the determination of the protection of the human subjects, the department **must** refer those changes back to the IRB for its approval before the research may commence. The IRB may require that proposed research be reviewed and approved by other appropriate University committees. The IRB must report any serious unanticipated problems involving risks to subjects or others to relevant University officials or committees, to any applicable sponsors or agencies, and to OHRP. The Director of the Office of Research Integrity may establish additional reporting relationships between the IRB and other officials or other committees, as deemed appropriate.

The IRB may be designated for research review under another institution's FWA (or other Assurance) only with the written agreement of the Institutional Official and in accordance with applicable Office of Research Oversight (ORO) requirements (for VA studies). Any such designation must be accompanied by a written agreement specifying the responsibilities of the facility and its IRB under the other institution's FWA (or other Assurance). The IRB has no authority over, or responsibility for, research conducted at other institutions in the absence of such a written agreement.

PROCEDURES:

IRB Chairperson. The Director of the Office of Research Integrity appoints the Chairperson. Examples of criteria for selection of the Chairperson are: (1) Comprehensive knowledge of the Human Research Protection Program, (2) Experienced researcher which can be validated by publications, (3) Uses sound ethical judgment which can be evidenced by past practices, and (4) Past experience as a chairperson or member of a patient care committee. The Chairperson serves a 3-year term and may be reappointed. He/She schedules and conducts the IRB meetings utilizing normal business practices. He/she ensures a quorum of voting members are present prior to voting on any agenda items, being

especially aware of quorum requirements when conflict-of-interests arise. The Chairperson, or his designee, signs all official IRB correspondence unless otherwise indicated.

IRB Members. The Director of the Office of Research Integrity appoints IRB members. Members serve 3-year staggered terms, and are eligible for reappointment. Members vote to approve, require modifications to, defer, or disapprove research submitted to the IRB. A more than fifty-percent quorum of voting members, including the Chairperson (or interim chair) and non-scientist member, must be represented at each meeting to vote on any research activity. Regular attendance at IRB meetings is essential; therefore, two unexcused absences or three excused absences within a 12-month period will be brought to the attention of the Director, ORI, for a determination as to whether an alternate is necessary. Members who serve as designee to the Chairperson for the conduct of expedited and exempt reviews are selected based on the following qualifications and experience:

- 1) Comprehensive knowledge of the Human Research Protection Program
- 2) Knowledge and understanding of the criteria for expedited and exempt review and
- 3) Experience in the particular field of research.

The IRB Membership must satisfy the following requirements:

- 1) Be comprised of at least five members.
- 2) Possess varying professional backgrounds to promote complete and adequate review of research activities commonly conducted at the institution.
- 3) Be sufficiently diverse relative to race, gender, cultural background, and sensitivity to community attitudes so as to promote respect for the IRB's advice and counsel in safeguarding the rights and welfare of human subjects.
- 4) Include persons able to ascertain the acceptability of proposed research in terms of institutional commitments, regulations, applicable law, and standards of professional conduct and practice
- 5) No IRB will consist entirely of members of one profession.
- 6) Include at least one member whose primary concerns are in scientific areas.
- 7) Have at least one member whose primary concerns are in non-scientific areas. A non-scientist member **must** always be present to have a quorum.
- 8) Include at least one member who is not otherwise affiliated with any of the institutions represented by the IRB and who is not part of the immediate family of a person who is affiliated with those same institutions.

Note: The non-scientific member and the non-affiliated member can be the same person. By the same token, a scientific member and the non-affiliated member can also be the same person as long as they meet the above requirements to represent each of those positions.

Review of VA research by IRB#1 (Medical) requires the inclusion as voting members, two or more VA employees (at least 5/8 time) who must be appointed as VA representatives by the VA Medical Center Director for a three year term. One of the VA representatives must have a scientific expertise. VA members serve as full members of the IRB and also review non-VA research matters coming before the IRB. VA members are appointed by the VA Medical Center Director for a 3 year term with no maximum number of terms.

Department of Education Research. For research funded by the National Institute on Disability and Rehabilitation Research, when an IRB reviews research that purposefully requires inclusion of children with disabilities or individuals with mental disabilities as research participants, the IRB must include at least one person primarily concerned with the welfare of these research participants.

Alternate IRB Members. The Director of the Office of Research Integrity can appoint one or more alternate members to replace regular IRB members who are, on occasion, unable to attend convened meetings of the IRB. Alternate members are listed on the IRB's official membership roster, which specifies which member the alternate is qualified to replace. The backgrounds of alternate members should be similar to the member they are replacing so that they are able to represent comparable interests. Terms of appointment, length of service, and duties are exactly the same as for regular IRB members. An alternate may be qualified to replace more than one regular member, but the alternate at any convened meeting may represent only one such member. When an alternate substitutes for a primary member, the alternate member will receive and review the same material that the primary member received or would have received.

Consultants. On an *as-needed* basis, the IRB may invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. The Director, ORI will identify and obtain a consultant. The consultants can either provide a written report to the IRB or attend a meeting. If a consultant provides a written report, that report will be provided to all IRB members and maintained in IRB records. If a consultant attends a meeting, the key information provided by consultants will be documented in the minutes. These individuals may not vote with the IRB. The IRB will be given the curriculum vitae or qualifications of the consultant in order to evaluate the weight to be given to the consultant's recommendations during protocol review. The Director, ORI has the responsibility to review the IRB member conflict of interest policy with each consultant to determine whether the consultant has a conflicting interest. If a conflict of interest exists then that consultant cannot be used.

IRB Coordinator. The IRB Coordinator distributes the agenda and research documents at least one week prior to the meeting, maintains the IRB membership roster and quorum requirements, and takes minutes of the meeting. The IRB Coordinator assures that the minutes are reviewed by the Chairperson and forwarded to the Director, ORI for approval, and finally made available to the Vice president of Research for his/her review. The approved minutes are distributed to the members of the IRB.

IRB Staff. The Director, ORI is responsible for the selection and appointment of all IRB staff. He/she will determine the requirements to be an IRB staff member. All IRB staff will complete the Collaborative Institutional Training Initiative (CITI) course, attend (when possible) the annual Public Responsibility In Medicine and Research (PRIMR) Conference, and any available subsequent training. The performance of the IRB staff will be evaluated by the Director, ORI on an annual basis.

Quorum Requirements and Voting. The IRB Coordinator is responsible to monitor the members present at convened meetings and determine that meetings are appropriately convened and remain so. Quorum requirements can be found in Chapter 16 IRB Documentation and Record Retention.

Should the quorum fail during the meeting (e.g., loss of a majority through recusal of members with conflicting interests or early departures, or absence of a nonscientist member), the IRB may **not** take further actions or votes unless the quorum can be restored.

Conflict of Interest. No IRB member may participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, **except** to provide information requested by the IRB. The IRB members, including the Chairperson, who have conflicting interests are required to disclose such interests and to recuse themselves from deliberations, quorum counts, and votes on the relevant protocol. Such absences are recorded in the meeting's minutes as recusal and not as abstentions. When an IRB member has been recused the minutes will reflect that the quorum has been maintained. The IRB must maintain a quorum if votes are taken during absences. For further information consult chapter 9 entitled **Conflict of Interest (IRB Members)**. IRB members are required to know the definition of a conflicting interest and to self-identify before the review of any protocol either at a convened meeting or using the expedited procedure.

Confidentiality. Local IRB Bylaws require an "IRB Member Non-Disclosure Agreement" to be signed by each member. This agreement will be renewed at intervals determined by the Director, ORI to ensure that all members are reminded that study materials provided to the IRB are proprietary and confidential. Study materials presented may not be discussed or distributed outside of official IRB business.

Procedures for Removal of Members. The IRB has authority to suspend or terminate the enrolment or ongoing involvement of human subjects in the facility's research as it determines necessary for the protection of those subjects. The IRB has the authority to observe or monitor the institution's human subject research to whatever extent it considers necessary to protect human subjects. Any IRB member may be removed for improper conduct, not acknowledging conflict-of-interest, and not maintaining confidentiality of the proceedings. In the event a member is charged with violating any of the above, the IRB will review the charges and the collected evidence and by a majority vote, not including the accused, will result in the recommendation to retain or remove the member from the Board. The IRB Chairperson will notify the Director, ORI in writing of the results of the IRB recommendation before he makes a final decision as to the removal. The accused member will be notified in writing and a copy will be submitted to the IRB.

Participant Input and Outreach. The Director, ORI is responsible for issues relating to participant input and outreach. The Director is to ensure the following:

- 1) Potential participants will be given information advising them of the ability to offer input, complaints, or concerns via the consenting process, ORI brochures or the OHRP pamphlet *Becoming a Research Volunteer*. This is the responsibility of the investigator and research staff for all studies in which informed consent has not been waived. All pamphlets will include local contact information. The ORI website also includes contact information for community input and concerns.
- 2) Participant outreach will be conducted by MU ORI and the VA Research Service. This outreach includes education to investigators and the community. Training sessions are conducted throughout the year for investigators and emphasize the use of community centers, Health Department activities, and hospital services to help reach the community for participant enrollment.
- 3) Distribution of informational pamphlets and display of posters will be reviewed annually. All pamphlets will include local contact information. Other possible outreach activities may include educational conferences with Veteran's groups and the community.
- 4) Educational items presented at the IRB meetings also include training for the members to provide input about community participation in studies. Continuing reviews include breakdowns (if tracked) of participants by gender, ethnic origin, vulnerable populations, mentally disabled, economically disadvantaged, and educationally disadvantaged. This allows the IRB to review the community demographics that are applicable to the study and discuss any issues.
- 5) Annually the Institutional Official and Director, ORI will evaluate participant outreach and implement changes as appropriate.

Chapter 18 - Non-Member Attendance at IRB Meetings

PURPOSE: To define the conditions in which non-Institutional Review Board (IRB) members (investigators and guests) may attend an IRB meeting and to establish guidelines for such participation. The procedures are designed to maintain the confidentiality of information shared as part of the activities of the IRB since unauthorized disclosure of any confidential information to any person or entity may cause irreparable harm to the parties protected.

POLICY: To maintain strict confidentiality of the issues discussed and the materials presented at IRB meetings and to require that certain requirements of guests be met before they may attend an IRB meeting.

SCOPE: This policy applies to all non-IRB Members who may have reason to attend an IRB meeting and the procedures to be followed to protect the confidentiality of the proceedings.

RESPONSIBILITIES:

Investigator: The primary- and secondary-reviewer team may request investigator attendance at the Marshall University Institutional Review Board (IRB) meeting in which his/her research is being reviewed. The principal reason for having the investigator at the meeting is to answer questions posed by the Board members in an effort to clarify minor ambiguities within the protocol and consent form so that delays in approving the protocol can be minimized. It is the IRB policy that investigators and members of the research team who attend the IRB meeting will do so after meeting the following criteria:

The investigator(s) and research team members (such as study coordinators) who will be attending must contact the IRB Administrative office at least two business days prior to the scheduled meeting date to confirm their scheduled appointment time. These appointments normally will occur in 10-15 minute increments. Note that scheduled times are not exact as some protocols may require more or less discussion than others.

The primary- and secondary-reviewer team will present the study to the board for discussion. Then the investigator and research team will be brought into the meeting given time to answer questions related to the study. IRB members are not limited in their presentation, discussion, or deliberation time. After the question period, the investigator and research team will be asked to leave the room until the discussion and vote are concluded. The investigator will be instructed as to when he/she may leave in case the IRB members have additional questions. The decisions by the IRB are sent to the investigator via IRBNet. No verbal answer regarding the status of the study is permitted during the meeting.

Guests: Guest attendance at the IRB meeting is for observance **only** and must be sponsored by a current IRB member. Guests who wish to observe the IRB meeting to learn about research such as students, new faculty members or staff who is not affiliated with a particular research protocol, or

visitors from other Institutional Review Boards (IRB) may attend the IRB meeting if the following criteria are met:

The guest's sponsor is required to contact the IRB Administrative office no later than 4pm on the Friday prior to the next scheduled meeting date to request consideration of their attendance. The Chairperson will make the decision concerning the request and the Sponsor (if applicable) will be notified. If the Chairperson approves the attendance of the individual, the individual is responsible for approaching the Chair to introduce themselves upon entering the room before the beginning of the IRB meeting. A non-disclosure agreement must be signed prior to the start of the meeting. Also, any individual may be asked to leave the meeting for speaking out in violation of the observance only rule or if the Chair determines a sufficient need.

An IRB Guest Non-Disclosure Agreement is available on the ORI website.

Chapter 19 - Primary and Secondary Reviewer System

PURPOSE: To conduct substantive and meaningful research protocol reviews by utilizing a Primary and Secondary Reviewer system.

POLICY: To utilize a primary and secondary reviewer system to ensure comprehensive protocol reviews are conducted by the convened IRB.

SCOPE: This policy covers all research activities undergoing the convened review process. Primary, and when applicable, secondary reviewers are utilized for initial reviews, continuing reviews, review of protocol changes, and review of reports of unanticipated problems involving risks to subjects or others. Primary reviewers may be utilized when there is a serious or continuing noncompliance issue involving a human subject protocol.

RESPONSIBILITIES:

IRB Chairperson – The IRB Chairperson is responsible for identifying primary and secondary reviewers based on the reviewer’s educational background, past experience, and board certification, if applicable. He/she assigns research protocols to be reviewed by the primary and secondary reviewers in a systematic manner.

Primary Reviewer - The primary reviewer is considered the lead reviewer on the IRB for research assigned to him/her. He/she is responsible for (1) being versed in the methodology and other aspects of the research; (2) conducting an in-depth review of the research and completing the Protocol Assessment checklist form provided; and (3) leading the discussion of the research at the convened meeting.

Secondary Reviewer - The secondary reviewer is also responsible for (1) being versed in the research methodology and other aspects of the research; (2) conducting an in-depth review of the research and completing the Protocol Assessment checklist form provided; and (3) discussing the protocol at the convened IRB meeting.

The Primary and secondary reviewers also have the responsibility evaluate whether a protocol involves categories of participants vulnerable to coercion or undue influence, and if so, then they should notify the IRB Chair so that he/she can ensure that one or more individuals who are knowledgeable about or experienced in working with these participants (as designated on the IRB roster) is present at the meeting.

IRB Members – The IRB members are responsible for serving as primary and secondary reviewers at the call of the Chairperson. All IRB members are expected to be familiar with each study to be reviewed at the meeting.

IRB Coordinator – The IRB coordinator is responsible for acquiring and maintaining resumes/curriculum vitae from members and consultants. The coordinator is responsible for documenting who is assigned to review the protocols and for assuring each reviewer receives the protocol package prior to the meeting.

PROCEDURES:

Initial Convened Review. The Chairperson works with the IRB Coordinator to assign primary and secondary reviewers based on the credentials and background of the reviewer in relation to the type of research protocol being reviewed. The Chairperson is responsible to ensure (as much as feasible) that at least one of these individuals will be present at the meeting and has the appropriate scientific and scholarly expertise to conduct an in depth review of the protocol. If such an IRB member cannot be identified, the Chairperson will defer the protocol review to another IRB with appropriate expertise or obtain consultation. The primary and secondary reviewers are given the following at least two weeks prior to the scheduled IRB meeting:

- full protocol application packet
- the full sponsor protocol
- clinical investigator's brochure (when one exists)
- application for funding support
- the Protocol Assessment Checklist
- any relevant grant applications
- the informed consent document(s)
- the complete DHHS-approved protocol (when one exists)
- recruitment materials (if applicable)

The reviewers are responsible for evaluating the material and conveying their evaluation to the IRB. The reviewer will utilize the Protocol Assessment Checklist submitted by the investigator to evaluate specific criteria outlined. The Protocol Assessment Checklist will be filed under each reviewer's comments on IRBNet.

Other IRB members are provided with the same essentials as the reviewers. All IRB members will be provided with materials for review at least one week prior to the scheduled IRB meeting. All IRB members who are not primary or secondary reviewers must review all provided materials in enough depth to be familiar with and prepared to discuss the information at the convened meeting. This material will include initial review, continuing review, and reviews requiring modifications to previously approved research. If an IRB member would like to obtain the information provided to a primary or secondary reviewer he/she can contact the Office of Research Integrity (ORI).

The primary or secondary reviewer can request that the principal investigator attend the IRB meeting to answer questions regarding the study. The reviewers will present the study to the board for discussion and express their concerns. Then the PI will be brought into the meeting to answer any questions posed by the IRB members. Prior to voting on the protocol, the PI will leave the room. The primary and secondary reviewers will make any additional comments concerning the protocol prior to voting. The PI will be notified of the results within 1 week of the IRB approval.

When review is conducted using the expedited procedure, at least one reviewer will receive and review all information that the convened IRB would receive.

Convened Continuing Review. The IRB conducts substantive and meaningful continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. Continuing reviews are conducted by the convened IRB unless the research falls into one or more of the categories appropriate for expedited continuing review.

Continuing reviews are conducted utilizing one primary reviewer. The Chairperson is responsible to ensure (as much as feasible) that the primary reviewer will be present at the meeting and has the appropriate scientific and scholarly expertise to conduct an in depth review of the protocol. If such an IRB member cannot be identified, the Chairperson will defer the protocol review to another IRB with appropriate expertise or obtain consultation. The primary reviewer has access to all previous study documents submitted on IRBNet and will be provided the following at least two weeks prior to the scheduled IRB meeting:

- the Continuing Review Assessment Form
- the Continuing Review Request Form
- the current consent form (or modified if applicable)
- the current educational certificates for all research staff
- any other new documentation

Two weeks prior to the convened meeting, the reviewer is provided with the above listed continuing review materials. Other IRB members are provided with the same essentials on IRBNet for review. All IRB members are required to review all materials in enough depth to be familiar with and prepared to discuss the information at the convened meeting.

Convened Review of Modifications to Previously Approved Research. For convened review of modifications to previously approved research the following is required:

- All IRB members will be provided all modified documents.
- At least one IRB member (e.g., primary reviewer) will conduct an in-depth review of all materials.
- All IRB members will review all provided materials in enough depth to be familiar with and prepared to discuss the information at the convened meeting.

Review is conducted using the Modification Protocol Assessment Form, and at least one reviewer will receive and review all information that the convened IRB receives. All IRB members will be provided with materials for the modification review one week prior to the scheduled IRB meeting.

When a convened IRB review of modifications is required, the IRB Chair is responsible to ensure that at least one IRB member with the appropriate scientific and scholarly expertise will conduct an in depth review of the protocol and be present at the meeting. If such an IRB member with appropriate expertise cannot be identified, the Chair will ask the Director, ORI to obtain consultation.

Chapter 20 - Quality Assurance/Quality Improvement (QA/QI)

PURPOSE: To provide guidance on the Quality Assurance/Quality Improvement Program for the Marshall University Human Research Protection Program (HRPP). The goal is to increase the quality and performance of the HRPP as well as to ensure compliance with federal regulations. The Quality Assurance (QA) portion of this program will assess the strengths and weaknesses of the HRPP and the Quality Improvement (QI) portion of the program will continually improve the performance of the HRPP.

POLICY: Our policy is to assess, monitor, and improve the performance of the HRPP, IRB, and the research activities. The key to performance improvement is the concept of continually striving to improve outcomes. The Office of Research Integrity is subject to periodic assessment for purposes of assuring the protection of human research subjects through compliance and quality improvement activities. Such assessments will determine the extent to which the HRPP complies with Federal regulations and its SOPs, and the adequacy of its processes and documentation.

SCOPE: This policy covers all aspects of Human Research Protection Program as well as research investigators and their staff. All research involving human subjects conducted at Marshall University, whether funded or unfunded, are within its purview.

RESPONSIBILITIES:

Office of Research Integrity is responsible to the Institutional Official for maintaining high standards throughout the facility's HRPP. These standards include those assuring the scientific quality of the research projects and the protection of human rights and safety. The Director, ORI conducts ongoing monitoring of the IRB by reviewing the IRB monthly minutes and conducting independent reviews. The Director will conduct a formal IRB review around the month of October each year and document the outcomes. Once the IRB review has been completed, the Director will meet with the Institutional Official to review the HRPP and to establish at least one goal for the upcoming year.

IRB Chairperson and the Director, Office of Research Integrity are jointly responsible for taking an active leadership role in performance improvement of the HRPP. They are responsible for developing an effective and systematic approach to assessing and improving the HRPP performance. The Director, ORI has the overall responsibility for the planning, development, staff orientation and education, conduct, validation and reporting of the outcomes of the quality improvement program for the MU HRPP. The Director, ORI is responsible for evaluating performance and adherence to applicable federal regulations, state laws and accreditation standards, which govern human research. The Director, ORI will also conduct an annual review of the organization's participant outreach activities and consider any changes that may be needed.

IRB Members, Investigators and their Research Staff are responsible for identifying opportunities for improvement and for participating in performance improvement activities.

IRB Coordinator maintains a file of quality improvement projects and activities. The data includes the area identified needing improvement, what action(s) taken to improve, and any results of QI activities. The IRB Coordinator will conduct training with investigators/coordinators on areas needing improvement. The IRB Coordinator will conduct a random study audit on a monthly basis. This audit should rotate between all the affiliated institutions and is documented using the audit checklist. All audit records are maintained for a period of 3 years from the date of the audit.

PROCEDURES:

IRB Activities. The IRB activities that may be monitored include but are not limited to:

- 1) **Informed Consent Documents.** The informed consent document review will be conducted during monthly study audits. The informed consent process including appropriate filing and documentation will be evaluated by the Director, ORI or his designee. The following items will be reviewed in the informed consent:
 - Presence or absence of all required elements (including IRB approval stamp)
 - Consent to be obtained prior to initiating research
 - Consent contains signature lines, initial lines and dates
 - Use of exculpatory language
 - Presence or absence of discrepancies between the protocol application and the informed consent document regarding the purpose, risks, and benefits of the research.

When evaluating the informed consent document the Director, ORI or his designee will give special consideration to documents approved for the following populations:

- Employees/Students
 - Homeless
 - Subjects likely to need surrogate consent
 - Subjects participating in high risk studies
- 2) **IRB Minutes.** The Director, ORI or his designee reviews the IRB minutes monthly and a thorough monitor is conducted annually. The minutes are monitored to assure compliance with regulations. The regulations require that minutes of IRB meetings be in sufficient detail to show:
 - Attendance at the meetings
 - Actions taken by the IRB
 - The vote on these actions including the number of members voting for, opposed, abstaining and the name of anyone recused
 - The basis for requiring changes in or disapproving research
 - A written summary of the discussion of controverted issues and their resolution
 - Consideration of additional safeguards for vulnerable subjects
 - Documentation of approval period
 - 3) **IRB SOP.** The Director, ORI or his designee will monitor new regulations and update the appropriate SOP accordingly. The Director ensures the newly updated SOP remains in compliance with the applicable federal regulations and institutional policies. This will be done

on a continuing basis and documented by a revision date in the SOP. The SOP will be reviewed and approved by the IO annually during the HRPP annual review.

- 4) Education. The IRB Coordinator will review the training records of the IRB members on an annual basis and the investigators and his/her research staff upon a study submission to assure compliance with the educational requirements.
- 5) Protocol and Application Packets. The IRB Coordinator will review individual IRB protocol files to ensure that there is documentation within each file of the IRB's actions and activities for that protocol.

Programs - Quality Assurance/Quality Improvement. The MU HRPP Quality Assurance Program periodically performs self-assessments and audits the research activities. The Quality Assurance approach includes the systematic collection and analysis, review of adverse outcomes, and resolution of individual problems. The QA program covers the utilization of self-assessment tools, the review of the SOP, and other monitoring tools to assess the performance in relation to the federal guidelines. The IRB evaluates effectiveness and conducts quality improvement activities on a continual basis.

Any problems identified are addressed and appropriate corrective action (e.g., change policy, procedure, communication, implements education or other such intervention) is taken to improve the process. The effects of the corrective action are assessed within a reasonable time frame to assure the action taken was effective. Any changes to the research activity, SAEs, Safety reports, protocol violations and non-compliance issues are reported and discussed at the IRB monthly meeting. Any urgent concerns are discussed immediately with the IRB Chairperson and the Director, ORI for their immediate attention. The IRBNet system tracks the information and maintains the electronic records in accordance with federal guidelines.

When the research protocol involves an investigational device, the IRB will monitor the storage, security, and dispensing of investigational devices to ensure compliance with policies. Any compliance violations will be investigated, corrected, and reported at the next monthly IRB meeting.

Investigators. The principal investigator (PI) is responsible for the conduct of the research study. He/she has the authority to delegate responsibility to members of the research team; however, the PI is ultimately responsible for the overall conduct of the study. If during routine QA/QI activities a PI or his staff is found to be in non-compliance with the federal regulations or institutional policies, the non-compliance will be reported to the IRB, the Director, ORI, and the Institutional Official.

The investigators and their staff are subject to periodic assessment for purposes assuring the protection of human research subjects. Monitors will include (1) consent process, (2) study conduct, and (3) compliance with applicable regulations, policies and guidelines. The results of these reviews will be used for purposes of quality improvement and actions taken, as needed.

- 1) **Consent Process.** The ethical conduct of human research is based upon the voluntary consent of the subject who has been appropriately informed about a study's risks and benefits. It is the responsibility of the investigator to ensure that all federal and state regulations have been met

through the language of the informed consent document, and that informed consent itself has been properly obtained from the subject or the subject's legal representative. Documentation of the informed consent process is required to establish that the subject was accurately and adequately informed and that no study-related procedures were initiated prior to obtaining informed consent. The Director, ORI or his designee will audit and evaluate the effectiveness of the consent process on a random basis, for selected active projects. This evaluation will include documentation that the following procedures have been followed:

- Consent has been obtained prior to initiating any research related procedures
- Only the IRB-approved consent form has been used
- The consent form has been signed and dated by the subject (or subject's legally authorized representative) and the individual providing the information to the subject
- The subject's case history documents the consent process with an appropriate note and original signed consent document
- There is documentation that the subject or the subject's legally authorized representative was provided a copy of the consent form

The survey and monitoring of informed consent is designed to improve the consent process, ensure compliance with federal regulations on informed consent and educate investigators and study staff about the informed consent process.

2) Study Conduct. Human subject selection must be in accordance with the inclusion/exclusion criteria to ensure maximal subject safety during the protocol. The safety and well-being of subjects is the primary concern. Close monitoring and careful assessment of subjects will enable the investigator to detect adverse events in the earliest stages and respond immediately with appropriate treatment. The research investigator and his staff must pay close attention to the subject's safety as well as to the integrity of the data collected. The Director, ORI or his designee monitors the protocols randomly by reviewing the following:

- Use of only IRB-approved advertisements and subject recruitment materials
- Adherence to inclusion/exclusion criteria
- Adherence to IRB-approved protocols and conditions
- Obtaining IRB approval prior to initiating changes to the protocol or consent form, except where necessary to eliminate apparent immediate hazards to subjects
- Reporting adverse events
- Reporting all unanticipated problems involving risks to human subjects
- Reporting all protocol deviations
- Reporting of protocol modifications

Special consideration is given to studies involving the following:

- Investigators with numerous studies
- New investigators
- Investigators with studies outside their normal therapeutic interest
- Vulnerable subjects
- Subjects likely to need surrogate consent
- Subjects participating in high risk studies

- 3) **Compliance.** The Principal investigator has the authority and responsibility for the ethical conduct of the study and compliance with federal regulations. Part II of the Initial Protocol Application contains the Certification and Assurance document that specifies the PI's compliance responsibilities. By signing the IRBNet submission, the PI agrees to comply with the federal guidelines upon which this document is based. The PI has the authority to delegate responsibility to members of his research team; however, he is ultimately responsible for the conduct of the study and compliance with federal regulations. If, during QA/QI activities, the PI is found not to be in compliance, the non-compliance will be reported to the IRB, Director of the Office of Research Integrity, the Institutional Official, and other appropriate University officials.

The Process Improvement Outcomes. The Director ORI will discuss the overall results of the process improvement investigations and study audits with the Institutional Official at the annual HRPP review. This annual review is documented and maintained by the Director ORI.

A copy of the annual HRPP review is available at ORI.

Chapter 21 - Recruitment and Selection of Human Subjects

PURPOSE: To provide guidance in the recruitment, selection, and payment of human subjects.

POLICY: To ensure that human subjects are recruited, selected, and, in certain cases, receive payment for their participation in research activities without being subjected to coercion or undue influence. Human subjects are given sufficient information about the research and its risks and benefits to reach an **informed decision** as to whether they will **voluntarily participate**. Adequate precautions must be taken to safeguard the privacy and the confidentiality of their information. Human subjects are informed of the extent to which confidentiality of research records will be maintained. The decision by human subjects not to participate may not jeopardize their ability to receive care, if applicable.

SCOPE: This policy covers all human subjects involved in research activities approved by the IRB.

RESPONSIBILITIES:

IRB Chairperson and Members are responsible for ensuring that the rights and welfare of research subjects are protected. They are responsible for ensuring recruitment, selection, and payment of human subjects is performed equitably, in a manner free from coercion, and undue influence. The IRB is responsible for ensuring the informed consent contains information sufficient for the subject to assess risks and benefits and the consent is written at the subject's level of understanding.

Principal Investigator is responsible for ensuring that human subjects are recruited, selected, and receive payment as deemed appropriate, in an environment free from coercion or undue influence. It is also his/her responsibility to ensure that the informed consent has sufficient information about the research and that the informed consent is written at a reading level the subject can understand. The risks and benefits are explained sufficiently for the human subject to reach an informed decision as to whether they will voluntarily participate. The investigator is responsible for explaining the subject's rights including his privacy and confidentiality.

PROCEDURES:

Advertisements and Recruitment Incentives. The IRB reviews advertisements, recruitment, and payment incentives associated with the research to ensure they are consistent with prohibitions on coercion and undue influence. The advertisement to recruit subjects must be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included:

- The name and address of the clinical investigator and research facility.
- The condition under study and the purpose of the research.
- In summary form, the criteria that will be used to determine eligibility for the study.
- The time or other commitment required of the subjects.
- The location of the research and the person or office to contact for further information.

- A clear statement that this is research and not treatment.
- The fact that the study has been approved by the IRB.

When reviewing advertisements, the IRB is required to review:

- The information contained in the advertisement
- The mode of its communication
- The final copy of printed advertisements
- The final audio/video tape taped advertisements

The IRB reviews advertising to assure that advertisements do not:

- State or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol.
- Make claims, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation.
- Make claims, either explicitly or implicitly, that the test article is known to be equivalent or superior to any other drug, biologic or device.
- Use terms such as "new treatment," "new medication" or "new drug" without explaining that the test article is investigational.
- Promise "free medical treatment" when the intent is only to say participants will not be charged for taking part in the investigation.
- Include exculpatory language.
- Emphasize the payment or the amount to be paid, by such means as larger or bold type.

The IRB evaluates the recruitment procedures to assure that informed consent is given freely and to avoid coercion or undue influence. They evaluate from what population the subjects will be drawn, what incentives are being offered, and the conditions under which the offer will be made.

Recruitment Procedure. The IRB requires a copy of all forms of advertisements to be submitted for review and approval prior to publication. This is one of the requirements for a protocol submission. A good way to avoid any possibility of coercion and to promote voluntary participation is to place flyers, posters, and brochures in public places and to advertise in newspapers and other local publications.

The recruitment material should include the following:

- investigator name and address
- purpose of the research
- eligibility criteria for participation in research study
- an accurate description of the benefits for the subject
- time required and any other commitments required of the subject
- location of research
- contact person for further information

The investigator must receive approval from the IRB before he/she reviews any medical charts, logbooks, or databases for potential subjects. The investigator may request information concerning the number of cases that may fit the study criteria in order for the investigator to determine if he can obtain a sample size large enough to support the research study. Investigators are not to request names from persons having access to records or databases in order for the PI to contact the potential subjects.

These subjects, if contacted, could perceive this action as an invasion of privacy and a breach of subject confidentiality.

An investigator may recruit his own patients, but if he plans recruiting another physician's patients, he should request the assistance of that physician to introduce the research protocol. The investigator can prepare an informational letter explaining the protocol and the potential subject's physician can deliver this letter. The letter should include the following:

- explain the research study
- tell who is conducting the study
- what the study is designed to investigate
- why the potential subject is being asked to participate (medical diagnosis, age, sex, etc.)
- whom to contact if interested in learning more about the study
- ask permission for the investigator to contact the subject directly

The personal physician would contact the investigator to give him the names of interested subjects. The IRB requires a draft of the above stated letter with the other required application materials.

Subject Selection. The IRB considers subject selection criteria in its review of research to ensure that the criteria are appropriate to the purposes of the research, the setting in which the research occurs, and the fair (equitable) distribution of the burdens, risks and benefits of the research. The IRB evaluates the potential benefits, burdens, and risks of the research. They also evaluate any inclusion or exclusion criteria, any scientific and ethical justification for including vulnerable populations such as children, prisoner, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons as well as the scientific and ethical justification for excluding classes of persons who might otherwise benefit from the research.

Additional safeguards for Department of Defense-sponsored research conducted with international populations include:

- The researcher has permission to conduct research in that country by certification, or local ethics review.
- The researchers follow all local laws, regulations, customs and practices.
- Additional safeguards might not be applicable to social-behavioral research involving no more than minimal risk.

Additional protections for military research participants to minimize undue influence include:

- Officers cannot influence the decision of their subordinates.
- Officers and senior non-commissioned officers cannot be present at the time of recruitment.
- Officers and senior non-commissioned officers have a separate opportunity to participate.
- When recruitment involves a percentage of a unit, an independent ombudsman must be present.

Payment to Research Subjects. The IRB reviews any proposed payments to research subjects associated with the research. Payments to research subjects may not be of such an amount as to result in coercion or undue influence on the subject's decision to participate. Payments may not be provided to subjects on a schedule that results in coercion or undue influence on the subject's decision to continue participation. For example, payment may not be withheld as a condition of the subject

completing the research. If the subject withdraws early, payment must be prorated to reflect the time and inconvenience of the subjects participation up to that point. Applications must include the amount and schedule of all payments.

Payment may be permitted, with prior approval of the IRB, in the following circumstances:

- No direct subject benefit and the standard of practice locally is to pay participants in this situation.
- Others being paid. In multi-institution studies, where subjects at a collaborating institution are to be paid for the same participation in the same study at the same rate proposed.
- Comparable situations. In other comparable situations in which, in the opinion of the IRB, payment of subject volunteers is appropriate.
- The participant will incur transportation expenses that would have been incurred in the normal course of receiving treatment and will not be reimbursed by another mechanism.

Payments to participants must meet the following criteria:

- Credit for payment must accrue as the study progresses and not be contingent upon the participant completing the entire study.
- Any amount paid as a bonus for completion must be reasonable and not so large as to unduly induce participants to stay in the study when they would otherwise have withdrawn.
- All information concerning payment, including the amount and schedule of payments, must be set forth in the consent document.
- The entire payment may not be contingent upon completion of the entire study.
- Compensation for participation in a trial offered by a sponsor may not include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

Investigators who wish to pay research subjects must indicate in their proposal the justification for such payment with reference to the criteria listed and, in addition, must:

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

The IRB reviews all proposals involving the payment of subjects (in excess of reimbursement for travel) in the light of these guidelines. The research office ensures that such payments to subjects are made from appropriate funds.

Payments in exchange for referrals of potential participants ("finder's fees") are prohibited. Also payments to the organization or research staff designed to accelerate recruitment that were tied to the rate or timing of enrollment ("bonus payments") are prohibited.

For VA research, participants cannot be paid to participate in research when the research was integrated with a patient's medical care and when it made no special demands on the patient beyond those of usual medical care. For VA participants, payment is limited to situations allowed by the VA.

Compensation for Injury. The IRB ensures that subjects are provided with accurate information about the availability of compensation and treatment for injury occurring in the research that it reviews. However, this requirement does not apply to (1) treatment for injuries due to non-compliance by a subject with study procedures; or (2) research conducted for Marshall University under a contract with an individual or other academic institution.

Fee Splitting. Compensation to PIs, physicians and other health care providers for identifying and /or enrolling subjects is considered “fee splitting” and must not occur.

Indemnity and Liability Provisions. Execution of an indemnity or liability agreement with an industry-sponsor or external collaborator requires the express approval of the Marshall University General Counsel, and is rarely permitted.

Compliance with All Applicable State and Local Law. All human subject research conducted at Marshall University or by the University’s employees or agents or otherwise under the auspices of the VA must comply with applicable state and local laws. The IRB should familiarize themselves with the requirements of all applicable state and local laws pertinent to the conduct of human subject research to ensure that the research it approves complies fully with all such requirements. The IRB SOP should reference applicable state and local law.

Voluntary Participation Statement. It is particularly important that subjects understand and have complete confidence that failure to participate **will not** jeopardize any University-provided care.

Informed consent information must contain clear statements of the following:

- Participation in the research is voluntary.
- Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.
- The subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Human subjects will be notified of significant new findings in generally within three (3) months of the release of the new findings by the research investigator or study coordinator.

ICH-GCP Specific Requirements of Investigators.

- When appropriate, the investigator informs the participant’s primary physician about the participant’s participation in the clinical trial if the participant has a primary physician and if the participant agrees to the primary physician being informed.
- Although a participant is not obliged to give his or her reasons for withdrawing prematurely from the clinical trial, the investigator should make a reasonable effort to ascertain the reason, while fully respecting the participant’s rights.

Department of Defense Research. When following DoD regulations and when research involves U.S. military personnel, limitations on dual compensation:

- Prohibit an individual from receiving pay of compensation for research during duty hours.

- U.S. military personnel may be compensated for research if the participant is involved in the research when not on duty.
- Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to \$50 for each blood draw.
- Non-Federal persons may be compensated for research participation other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.
- Civilian investigators attempting to access military volunteers should seek collaboration with a military investigator familiar with service-specific requirements.

Department of Justice Research. When following DOJ regulations and for research conducted within the Bureau of Prisons:

- The selection of participants within any one organization must be equitable.
- Incentives may not be offered to help persuade inmate participants to participate. However, soft drinks and snacks to be consumed at the test setting may be offered.
- Reasonable accommodations such as nominal monetary recompense for time and effort may be offered to non-confined research participants who are both:
 - No longer in Bureau of Prisons custody.
 - Participating in authorized research being conducted by Bureau employees or contractors.

When Following VA Regulations:

- The IRB must consider the relevance of the research to the mission of the VA and the Veteran population it serves.
- A VA facility may not use Facebook as a method of advertising non-VA studies.
- Research team members are prohibited from requesting social security numbers by telephone.

Chapter 22 - Reporting Policy

PURPOSE: To establish reporting guidelines for the Marshall University Human Research Protection Program (HRPP)

POLICY: In accordance with 38 CFR 16.103 and the Common Rule, this policy provides the policy for reporting procedures.

RESPONSIBILITIES:

The Director, ORI will report to the Institutional Official (IO) and regulatory agencies when:

- The IRB determines that a problem is an unanticipated problem involving risks to participants or others.
- The IRB determines that non-compliance is serious or continuing non-compliance.
- The IRB or anyone in the organization suspends or terminates IRB approval.

PROCEDURES:

Preparation of the Report.

- The Director, ORI drafts the report.
- The Institutional Official approves the report.

What to Include in the Report:

- 1) For unanticipated problems involving risks to subjects or others:
 - (a) Name of the institution (e.g., university, hospital, foundation, school, etc) conducting the research;
 - (b) Title of the research project and/or grant proposal in which the problem occurred;
 - (c) Name of the principal investigator on the protocol;
 - (d) Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);
 - (e) A detailed description of the problem; and
 - (f) 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.).
- 2) For serious or continuing noncompliance (as defined in Chapter 6):

- (a) Name of the institution (e.g., university, hospital, foundation, school, etc) conducting the research;
- (b) Title of the research project and/or grant proposal in which the noncompliance occurred;
- (c) Name of the principal investigator on the protocol;
- (d) Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);
- (e) A detailed description of the noncompliance; and
- (f) Actions the institution is taking or plans to take to address the noncompliance (e.g., educate the investigator, educate all research staff, suspend the protocol, suspend the investigator, conduct random audits of the investigator or all investigators, etc.).

Note: Determinations of serious or continuing non-compliance of DoD-supported research must be promptly (no longer than within 30 days) reported to the DoD human research protection officer.

3) For suspension or termination:

- (a) Name of the institution (e.g., university, hospital, foundation, school, etc) conducting the research;
- (b) Title of the research project and/or grant proposal that was suspended or terminated;
- (c) Name of the principal investigator on the protocol;
- (d) Number of the research project assigned by the IRB that was suspended or terminated and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);
- (e) A detailed description of the reason for the suspension or termination; and
- (f) The actions the institution is taking or plans to take to address the suspension or termination (e.g., investigate alleged noncompliance, educate the investigator, educate all research staff, require monitoring of the investigator or the research project, etc.)

Distribution of the Report. The Director ORI will send copies of the approved report to:

- 1) The IRB by including the letter in the next agenda packet as an information item.

- 2) The Institutional Official.
- 3) The following agencies: (Reporting is not required if the problem occurred at a site that was not subject to the direct oversight of the organization, or the agency has been notified of the event by other mechanisms.)
 - (a) OHRP.
 - (b) FDA, if the study is subject to FDA regulations.
 - (c) Any “Common Rule” Federal Agency that is supporting the research.
 - (d) For VA research: the Research and Development Coordinator will be sent a copy of the report and will then be responsible for all VA specific reporting.

Time Frame for Reporting Incidents. The Director, ORI will ensure that all steps of this policy will be completed within 15 days of the initiating action. For more serious actions, the Director, ORI may expedite reporting. **VA reporting will be in accordance with the Hershel Woody Williams VAMC Reporting SOP.**

Department of Defense Reporting. When following DoD regulations the following shall be promptly (no longer than within 30 days) reported to the DoD human research protection officer:

- When significant changes to the research protocol are approved by the IRB.
- The results of the IRB continuing review.
- Change of reviewing IRB.
- When the organization is notified by any Federal department, agency or national organization that any part of the HRPP is under investigation for cause involving a DoD-supported research protocol.

AAHRPP Reporting Requirements. The Director, ORI will report to AAHRPP as soon as possible but generally within 48 hours after the organization or any researcher (if the researcher is notified rather than the organization) becomes aware of:

- (i) Any negative actions by a government oversight office, including, but not limited to OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated, FDA Restrictions Placed on IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections.
- (ii) Any litigation, arbitration, or settlements initiated related to human research protections.
- (iii) Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding the organization’s HRPP.

Chapter 23 - Risk and Benefits

PURPOSE: To establish guidelines for the Institutional Review Board (IRB) to assess the risks and benefits in human subject research activities.

POLICY: To systematically evaluate the overall level of risk and anticipated benefits as part of the initial review and continuing review of all research involving human subjects.

SCOPE: This policy covers all research involving human subjects.

DEFINITIONS:

Risk is an injury to safety, rights, or welfare and it is expressed in terms of probability, magnitude, and permanency. Types of risk are physical, economic or financial, social, psychological, and legal.

- 1) Physical risk – actions and situations that result in bodily harm.
- 2) Economic or financial risk – loss of privacy could lead to loss of benefits, insurance, or employment.
- 3) Social - specific uses of information could hurt the subject's social position (reputation) or could be harmful to groups of subjects in their community.
- 4) Psychological - deception or mishandling of information could cause psychological trauma.
- 5) Legal - the risk that a research participant's sharing of information may be self-incriminating, resulting in civil or criminal liability.

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.

In the case of research involving prisoners as participants, 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.

RESPONSIBILITIES:

Institutional Official – As the Institutional Official (IO), the Marshall University Vice President for Research has the ultimate responsibility to ensure the rights and safety of human subjects are protected. The Institutional Official delegates the authority to the IRB to systematically evaluate the overall risks and benefits for the human subjects to assure they are protected.

IRB Chairperson – The Chairperson has the responsibility to ensure all research involving human subjects is systematically evaluated as to the risks and benefits. No research activity will be approved where the risks are not reasonable in relation to the benefits to the subject and the knowledge to be gained. The Chairperson assures continual monitoring of the risks and benefits throughout the research activity. The Chairperson is responsible for reporting any serious unanticipated problems involving risks to subjects or others to the Director, ORI and to any applicable sponsors or agencies.

IRB Members – The members have the responsibility to systematically evaluate all research involving human subjects as to the risks and benefits involved and only approve those research activities that are reasonable in relation to the benefits. Therefore, scholarly or scientific review of proposed research should answer the following questions:

- 1) Does the research use procedures consistent with sound research design?
- 2) Is the research design sound enough to reasonably expect the research to answer its proposed question?
- 3) What is the importance of the knowledge expected to result from this research?

Principal Investigator (PI) – The Principal Investigator has the responsibility to present his true evaluation of the risks and benefits of the research activity and he **must report** any new information concerning risks to the human subjects **promptly** to the IRB. The PI is responsible for ensuring and documenting that the patient can differentiate between those activities that are therapeutic in nature from research activities.

IRB Coordinator – The IRB Coordinator has the responsibility to ensure all risks identified are properly documented in the IRB minutes and for preparing any reports to higher level authorities or agencies.

PROCEDURES:

Distinguishing Differences in Types of Risk. The IRB must distinguish research that is greater than minimal risk from research that is no greater than minimal risk when considering human subject research activities. Research that is no greater than minimal risk may be eligible for expedited review, waiver or alteration of informed consent requirements, or waiver of the requirement to obtain written documentation of consent (Waiver of informed consent is not generally appropriate for FDA regulated test articles.)

To approve a research activity, the IRB must comply with the following regulatory criteria:

- 1) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:
 - (a) 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.
- (b) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may 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 that 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.
- (c) 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, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.
- (d) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with CFR §46.116 and any other applicable federal regulations.
- (e) Informed consent will be appropriately documented, in accordance with and to the extent required by CFR §46.117 and any other applicable federal regulations.
- (f) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- (g) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- 2) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.
- 3) In order to approve research in which some or all of the subjects are children, an IRB must determine that all research is in compliance with CFR §46, subpart D.

Criteria That The IRB Uses To Determine Which Research Requires Review More Often Than Annually. The IRB may require review more often than annually when any of the following are true:

- 1) Procedures not before used in humans.
- 2) More than minimal risk to vulnerable populations with no prospect of direct benefit.
- 3) A high likelihood that participants will die due to the research procedures.
- 4) Any other reason for which the IRB wants closer monitoring.

In specifying an approval period of less than 1 year, the IRB may define the period with either a time interval or a maximum number of subjects, (i.e., after 3 months or after three subjects). The IRB will determine the time interval or number of subject and the IRB minutes will clearly reflect these determinations regarding risk and approval period.

Criteria That The IRB Uses To Determine Which Research Requires Verification From Sources Other Than The Investigator That No Material Changes Have Taken Place Since The Last IRB Review. The IRB will get verification from sources other than the investigator that no material changes have taken place since the last review when any of the following are true:

- 1) The information provided by the investigator is internally inconsistent or inconsistent with other information known to the IRB, and the inconsistency cannot be resolved through communication with the investigator.
- 2) The IRB doubts the information provided by the investigator.
- 3) The investigator has a history of non-compliance with applicable continuing review.
- 4) Any other reason for which the IRB wants verification.

If yes, then verification must be obtained from sources other than the investigator that no material changes have occurred since the last IRB review.

The IRB can obtain verification that no material changes have taken place since the last review by audit or official notification from the institutional official of the site in which the research is being conducted.

Continual Review. The IRB continually reviews Serious Adverse Events (SAE) reports, sponsor safety reports, changes in the investigator brochures, changes to the research, including amendments to the protocol, any information that may change the risk/benefit ratio, most recent findings, including summary of subject experiences (benefits, adverse reactions) and summary of DSMB meetings (if applicable), reports of injuries to subjects, unanticipated problems involving risks to subjects and subjects withdrawn and the reasons for withdrawal.

Privacy and Confidentiality. To approve research, the IRB determines that there are adequate provisions to protect the privacy of subjects and the confidentiality of data. In reviewing confidentiality protections, the IRB considers the nature, probability, and magnitude of harms that

would be likely to result from a disclosure of collected information outside the research. It evaluates the effectiveness of proposed anonymity techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections. More information concerning Privacy and Confidentiality or Safeguarding Confidentiality can be found in Chapter 7 of this SOP.

Certificates of Confidentiality. Where research involves the collection of highly sensitive information about individually identifiable subjects, the IRB may determine that special protections are needed to protect subjects from the risks of investigative or judicial processes. In these situations the IRB may require that an investigator obtain a Department of Health and Human Services (DHHS) Certificate of Confidentiality (CoC). For studies not funded by DHHS, if there is an Investigational New Drug Application (IND) or an Investigational Drug Exemption (IDE), the sponsor can request a CoC from the FDA. The CoC protects against the involuntary release of sensitive information about individual subjects for use in Federal, state, or local civil, criminal, administrative, legislative, or other legal proceedings. The CoC does not prohibit voluntary disclosure of information by an investigator, such as voluntary reporting to local authorities of child abuse or of a communicable disease. In addition, the CoC does not protect against the release of information to VA, DHHS or FDA for audit purposes. The IRB requires that these conditions for release be stated clearly in the informed consent document.

Safeguards for Vulnerable Subjects. The IRB must determine that additional safeguards have been included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, persons with mental disabilities, or economically or educationally disadvantaged persons.

The IRB pays special attention to the following specific elements of the research plan when reviewing research involving vulnerable subjects:

- 1) Inclusion and exclusion criteria for selecting and recruiting subjects; informed consent and willingness to volunteer; coercion and undue influence; and confidentiality of data.
- 2) Group characteristics, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable subjects.
- 3) Adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and informed consent or assent. When weighing the decision whether to approve or disapprove research involving vulnerable subjects, the IRB looks to see that such procedures are a part of the research plan. In certain instances, it may be possible for researchers to enhance understanding for potentially vulnerable subjects. Examples include requiring someone not involved in the research to obtain the consent, the inclusion of a consent monitor, a subject advocate, interpreter for hearing-impaired subjects, translation of informed consent forms into languages the subjects understand, and reading the consent form to subjects slowly and ensuring their understanding.

- 4) The IRB is required to document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent.

Compensation for Injury. The IRB ensures that subjects are provided with accurate information about the availability of compensation and treatment for injury occurring in the research that it reviews. However, this requirement does not apply to (1) treatment for injuries due to non-compliance by a subject with study procedures; or (2) research conducted for Marshall University under a contract with an individual or another academic institution.

Review of Reports of Unanticipated Problems or Serious Adverse Events (SAE). Refer to Chapter 12 of this SOP for information on this topic.

Suspension or Termination of IRB Approval of Research. 45 CFR 46.113 states the following: *"An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head."*

- 1) Suspension of previously approved research. Suspension of IRB approval: An action taken by the IRB to temporarily or permanently withdraw approval for some or all research activities short of permanently withdrawing approval for all research activities.
- 2) Termination of previously approved research. Termination of IRB approval: An action taken by the IRB to permanently withdraw approval for all research activities.

Circumstances under which the IRB may suspend or terminate previously approved research:

- 1) When research is not conducted in accordance with IRB requirements.
- 2) When research is associated with unexpected serious harm to participants.

The IRB utilizes the following process to suspend or terminate previously approved research:

- 1) The IRB Chairperson is authorized to make suspension and termination determinations.
- 2) The IRB Chairperson will evaluate all possible suspensions and terminations on an urgent basis.
- 3) When a termination or suspension involves the withdrawal of current participants from the research:
 - (a) Enrolled participants will be notified;

- (b) The withdrawal of enrolled participants must take into account their rights and welfare; and
- (c) When follow-up of participants for safety reasons is permitted or required, participants will be so informed and any adverse events or unanticipated problems involving risks to participants or others will be reported to the IRB and others as required by the protocol and organizational policies and procedures.

It is the responsibility of the Director, ORI to provide prompt written notification to institutional officials and regulatory agencies when:

- 1) It has been determined that an incident of non-compliance is serious or continuing.
- 2) It has been determined that an event is an unanticipated problem.
- 3) The IRB suspends or terminates its approval of research.

The Director, ORI is also responsible for the reporting of:

- 1) All events involving VA research to the VA Research and Development Office and the VA Office of Research Oversight.
- 2) Unauthorized use, loss, or disclosure of individually identifiable information.
- 3) Violations of information security requirements to the appropriate Information Security Officer.

Social and Psychological Harms. Behavioral and Social Sciences research often involves surveys, observational studies, personal interviews, or experimental designs involving exposure to some type of stimuli or intervention. IRB carefully determines the probability of risk of harm to subjects and considers the following:

- 1) The potential for subjects to experience stress, anxiety, guilt, or trauma that can result in genuine psychological harm.
- 2) The risks of criminal or civil liability or other risks that can result in serious social harms, such as damage to financial standing, employability, insurability, or reputation; stigmatization; and damage to social or family relationships.
- 3) If information is being collected on living individuals other than the primary “target” subjects and the risk of harm to those “non-target” individuals, as well.

To mitigate such risks, IRB reviews the proposal for appropriate preventive protections and debriefings, adequate disclosure of risks in the informed consent information, and mechanisms to protect the confidentiality and privacy of persons participating in or affected by the research.

Research Involving Deception or Withholding of Information. The reviewing of research involving incomplete disclosure or outright deception must apply both common sense and sensitivity to the review. Where deception is involved, the IRB needs to be satisfied that the deception is necessary and that, when appropriate, the subjects shall be debriefed. (Debriefing may be inappropriate, for example, when the debriefing itself would present an unreasonable risk of harm without a corresponding benefit.) The IRB should also make sure that the proposed subject population is suitable. Deception can only be permitted where the IRB documents that a waiver of the usual informed consent requirements is justified under the criteria present in §46.116.

In making the determination to approve the use of deception under a waiver of informed consent, the IRB will consider each criterion in turn, and document specifically (in the minutes of its meeting and in the IRB protocol file) how the proposed research satisfies that criterion. (*Note: The regulations make no provision for the use of deception in research that poses greater than minimal risks to subjects*).

Research Involving Potentially Addictive Substances. Research involving potentially addictive substances often involves the use of what may be termed “abuse-labile” substances. Abuse-labile substances are pharmacological substances that have the potential for creating abusive dependency. Abuse-labile substances can include both legal and illicit drugs. The following are among the issues that the IRB should consider when reviewing research involving potentially addictive substances:

- 1) The subjects’ capacity to provide continuous informed consent, ensuring that subjects are competent and are not coerced.
- 2) If such research involves subjects that are institutionalized, the subjects’ ability to exercise autonomy could be impaired.
- 3) Consider the requirements for equitable selection of subjects and protections for maintaining confidentiality, as such a population may be at risk for being discriminated against, or over-selected.
- 4) Be sensitive to the ethical context of the research, in that there may be moral dilemmas associated with the use of placebos, or in cases where addicts are presented with alcohol or drugs.

Chapter 24 - Types of Research and Types of Reviews Conducted by the IRB

PURPOSE: To define the different types of research and to explain the various types of research activities conducted at this facility and the three types of reviews the IRB may conduct in considering the research activities.

POLICY: To ensure that the appropriate type of IRB review is conducted within the constraints of the federal regulations and the facility's policies and procedures.

SCOPE: This policy covers all research protocols conducted within the auspices of this IRB.

DEFINITIONS:

Human Subject Research - Under this organization's policy Human Subject Research is defined as

- Any activity that meets the DHHS definition of "research" and involves "human subjects" as defined by the DHHS regulations; OR
- any activity that meets the FDA definition of "research" and involves "human subjects" as defined by the FDA regulations.

Research – is defined in Chapter 1 “Introduction” of this SOP.

Human subject – is defined in Chapter 1 “Introduction” of this SOP.

Private information - includes information that an individual can reasonably expect will not be made public, and information about behavior that an individual can reasonably expect will not be observed or recorded. Private information must be individually identifiable.

Identifiable - means that the identity of the individual is or may readily be ascertained by the investigator or associated with the information.

Adverse Event (AE) - is defined in Chapter 12 “Ensuring Prompt Reporting of Unanticipated Problems Involving Risks to Participants or Others” of this SOP.

Case Studies/Presentations - Case studies/presentations which are published and/or presented at national or regional meetings are often **not** considered human subject research if the case is limited to a description of the clinical features and/or outcome of a single patient and do not contribute to generalizable knowledge (Note: a comparison of case studies would qualify as human subject research). In this situation, no IRB notification or classification should be required since it is not human research for IRB purposes. Of course, if an investigator is unsure whether an activity is human research or not, he/she should contact the Office of Research Integrity (304) 696-4303 for a judgment on that point.

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.

In the case of research involving prisoners as participants, 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.

Research that is no greater than minimal risk may be eligible for expedited review, waiver or alteration of informed consent requirements, or waiver of the requirement to obtain written documentation of consent. Waiver of informed consent is not generally appropriate for FDA regulated test articles.

Note: When following Department of Defense regulations the definition of minimal risk based on the phrase “ordinarily encountered in daily life or during the performance of routine physical or physiological examination or tests” shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain.)

Minor change is one that makes no substantial alteration in:

- the level of risks to subjects;
- the research design or methodology;
- the number of subjects enrolled in the research;
- the qualifications of the research team;
- the facilities available to support safe conduct of the research;
- the addition of procedures not included in categories (1)-(7) of research that can be reviewed using an expedited procedure; or
- any other factor, which would warrant review of the proposed changes by the convened IRB.

If a modification is the addition of an investigative site it will be treated as any modification to a study and must be submitted for Expedited or Convened review. If the IRB Chair determines that the amendment falls into the category of a minor change as listed above then it will receive an Expedited review, and if not then the amendment will go to the convened board. This would be treated as an external site relying on our IRB. If the new investigative site has an IRB then a reliance agreement would need to be signed, and if not then a letter would be needed indicating their willingness to participate in the study.

RESPONSIBILITIES:

IRB Chairperson is responsible for ensuring that the appropriate type of review is conducted within all federal regulations and facility’s policies and procedures.

IRB Members are responsible for ensuring the reviews are conducted appropriately, ethically, and within the constraints of the federal regulations and station policies.

Principal Investigator (PI) is responsible for ensuring that every research subject's rights, welfare and safety are protected. He is responsible for the protocol design, which must minimize risks to subjects while maximizing benefits. The PI must ensure that all members of the research team always comply with the findings, determinations, and requirements of the IRB. He must also ensure the adequacy of both the informed consent process, regardless of which members of the research team are authorized to actually obtain and document consent.

IRB Coordinator is responsible for maintaining documentation of the activities of the IRB and reporting the information at the next IRB meeting.

Monitor - The following applies when following Department of Defense (DoD) regulations:

- The monitor may be an ombudsman or a member of the data safety monitoring board. The IRB must approve a written summary of the monitors' duties, authorities, and responsibilities.
- The IRB or HRPP official shall communicate with research monitors to confirm their duties, authorities, and responsibilities.
- The duties of the research monitor are determined on the basis of specific risks or concerns about the research, such as:
 - Perform oversight functions (e.g. observe recruitment, enrollment procedures, and the consent process, oversee study interventions and interactions, review monitoring plans and unanticipated problems involving risks to participants or others, oversee data matching, data collection and analysis).
 - Discuss the research protocol with researchers, interview human subjects, and consult with others outside of the study.
 - Report observations and findings to the IRB or a designated official.

TYPES OF RESEARCH:

The following are examples of various types of research; however, not all of these types of research are conducted at this facility.

- 1) **Clinical Research** involves research (a) to increase scientific understanding about normal or abnormal physiology, disease states, or development and (b) to evaluate the safety, effectiveness or usefulness of a medical product, procedure, or intervention. Vaccine trials, medical device research, and cancer research are, for example all types of clinical research.
- 2) **Behavioral and Social Sciences Research** involving human subjects focuses on individual and group behavior, mental processes, or social constructs and usually generates data by means of surveys, interviews, observations, studies of existing records, and experimental designs involving exposure to some type of stimulus or environmental intervention.
- 3) **Epidemiological Research** targets specific health outcomes, interventions, or disease states and attempts to reach conclusions about cost-effectiveness, efficacy, efficiency, interventions,

or delivery of services to affected populations. Some epidemiological research is conducted through surveillance, monitoring, and reporting programs; whereas, other epidemiological research may employ retrospective review of medical, public health, or other records.

- 4) **Repository Research, Tissue Banking, and Databases.** Research utilizing stored data or materials (i.e., cells, tissues, fluids, and body parts) from individually identifiable living persons qualifies as human subject research, and requires IRB review.
- 5) **Quality Assurance/Quality Improvement Activities.** Quality assurance activities attempt to measure the effectiveness of programs or services. Such activities may constitute human subject research, and require IRB review, if they are designed or intended to develop or contribute to generalizable knowledge and involve human subjects. Quality assurance activities that are designed solely for internal program evaluation purposes, with no external application or generalization, will probably not require IRB review. Individuals who incorrectly determine or assume that an activity is not human subject research will be considered noncompliant with the federal regulations. Where there is any doubt about whether an activity is human subject research the activity should be submitted to the IRB for a determination. Only the IRB can make an authoritative determination about whether an activity is human subject research.
- 6) **Pilot Studies** involving human subjects require IRB review.
- 7) **Human Genetic Research.** Genetic studies include but are not limited to: (a) pedigree studies (to discover the pattern of inheritance of a disease and to catalogue the range of symptoms involved); (b) positional cloning studies (to localize and identify specific genes); (c) DNA diagnostic studies (to develop techniques for determining the presence of specific DNA mutations); (d) gene transfer research (to develop treatments for genetic disease at the DNA level); (e) longitudinal studies to associate genetic conditions with health, health care, or social outcomes; and (f) gene frequency studies. The primary risks involved in the first three types of genetic research are risks of social and psychological harm, rather than risks of physical injury. Genetic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. For many genetic research protocols, these psychosocial risks can be significant enough to warrant careful IRB review and discussion. Those genetic studies limited to the collection of family history information and blood drawing are not automatically classified as "minimal risk" studies qualifying for expedited IRB review. Confidentiality is a major concern in determining if minimal risk is involved. The IRB must consider if informed consent from third parties can be waived and if so, document that reasoning in the IRB minutes. In most cases waiver of consent may be appropriate.
- 8) **Studies of Investigational Drugs or Biologics.** The FDA requires various stages of human subject research to ensure that drugs and biologics are both safe and effective for the proposed use. This safety and efficacy data may eventually be used in marketing materials or on the drug's label or patient insert.

- (a) **Phase One Drug Trials.** Phase 1 drug trials include the initial introduction of an investigational new drug into humans. These studies are typically closely monitored and conducted with healthy volunteers; sometimes, where the drug is intended for use in patients with a particular disease, however, such patients may participate as subjects. Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase 1 trials is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects involved in Phase 1 investigations is generally in the range of 20-80.
- (b) **Phase Two Drug Trials.** Phase 2 trials include controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well controlled, closely monitored, and conducted with relatively larger numbers of subjects (100-300).
- (c) **Phase Three Drug Trials.** Phase 3 drug trials involve the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, effectiveness, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug, and to provide an adequate basis for physician labeling. In Phase 3 studies, the drug is used in the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to the FDA for approval to market the drug. Phase 3 trials usually involve several hundred to several thousand patient-subjects. These studies are conducted with large groups of subjects (1,000-3,000).
- (d) **Phase Four Drug Trials.** Concurrent with marketing approval, the FDA may seek agreement from the sponsor to conduct certain post-marketing (Phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

- 9) **Department of Defense Research.** When following DOD regulations the following applies:
 - For non-exempt research, the IRB considers the scientific merit of the research.
 - The IRB may rely on outside experts to provide an evaluation of the scientific merit.
- 10) **Department of Justice Research.** When research is conducted within the Bureau of Prisons, the project must have an adequate research design and contribute to the advancement of knowledge about corrections.
- 11) **When following DoD requirements:** Research involving experimental subjects as defined in DODI 3216.02 is a subset of research involving human participants.

PROCEDURES:

All human subject research conducted at Marshall University or by Marshall University employees or agents or otherwise under the auspices of Marshall University must be prospectively reviewed. The ORI Director, IRB Chairperson or a designee who is an IRB member will determine if studies qualify for an exempted review. The chairperson (or his/her designee) will determine if studies qualify for expedited review. The chairperson retains the right to require a convened review for exempted or expedited studies when warranted by the nature of the research. Regardless of the type of review the investigator is notified in writing of the IRB's determinations.

Epidemiological Research - epidemiological research that involves aggregate examination of data without individually identifiable information is generally not human subject research. If the PI is in doubt as to whether or not their study is human subject research he/she should submit an abstract to the IRB#1 Chair for a determination.

Repository Research, Tissue Banking, and Databases. In the event, when data or materials are stored in a bank or repository for use in future research projects, the IRB will review the protocol detailing any repository policies and procedures for obtaining, storing, and sharing its resources, for verifying informed consent provisions, and for protecting subjects' privacy and maintaining the confidentiality of data. The IRB will establish standard operating procedures and then determine the parameters under which the repository may share its data or materials with or without IRB review of individual research protocols.

Types of Reviews. The IRB conducts three types of reviews: (1) Exempt, (2) Expedited, or (3) Convened.

Exempt Review. The Exempt determination will be made by the ORI Director, IRB Chair or his/her designee. A limited IRB review must be conducted by the IRB Chair or his/her designee. To obtain exempt status the research activity must meet one of the below listed categories.

(Note: There are several references to a **limited IRB review**. A limited IRB review is conducted by the IRB Chair/Designee (IRB member) to ensure that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. Studies that qualify under Exempt categories 2, 3, 7, and 8 may require a limited IRB review. The study is processed like an Exempt

study but the review must be conducted by the IRB Chair/Designee. If an IRB member reviewing the research by limited IRB review finds that research is greater than minimal risk, the reviewer must document the rationale for this determination and the rationale for review by the convened IRB. The IRB member conducting limited IRB review may not disapprove research and Marshall University retains the authority to suspend or terminate IRB approval of research approved with a limited review.)

- (1) Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
- (2) Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:
 - i. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
 - ii. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
 - iii. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).
- (3) Research involving benign behavioral interventions:
 - i. Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:
 - (a) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
 - (b) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
 - (c) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through

- identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).
- ii. For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.
 - iii. If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.
- (4) Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:
- i. The identifiable private information or identifiable biospecimens are publicly available;
 - ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;
 - iii. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or
 - iv. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.
- (5) Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to

those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended. There must also be no statutory requirement that an IRB review the research and the research must not involve significant physical invasions or intrusions upon the privacy of subjects.

- i. Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal website or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

(6) Taste and food quality evaluation and consumer acceptance studies:

- i. If wholesome foods without additives are consumed, or
- ii. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the 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.

(7) Storage or maintenance for secondary research for which broad consent is required:

Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §46.111(a)(8).

(8) Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:

- i. Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §46.116(a)(1) through (4), (a)(6), and (d);
- ii. Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §46.117;
- iii. An IRB conducts a limited IRB review and makes the determination required by §46.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (i) of this section; and
- iv. The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

Expedited Review. The IRB may use the expedited review procedure to review the following:

- Some or all of the research appearing on the list titled "Categories of Research That May be Reviewed by The Institutional Review Board (IRB) Through an Expedited Review Procedure," unless the reviewer determines that the research involves more than minimal risk;
- Minor changes in previously approved research during the period for which approval is authorized; or
- Research for which limited IRB review is a condition of exemption under §46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7) and (8).

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers 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 in §46.108(b). If a reviewer finds that research appearing on the expedited review list is greater than minimal risk, the reviewer must document the rationale for this determination and the rationale for review by the convened IRB.

Investigators **must** report to the IRB any proposed changes in the IRB-approved research, including proposed changes in informed consent documents. **No changes** may be initiated **without prior** approval of the IRB, except where necessary to eliminate apparent immediate hazards to subjects. The FDA can restrict, suspend, or terminate the IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

The investigator must complete the IRB Protocol Application Packet, which includes a checkbox to request expedited status. The IRB Chairperson or his designee reviews the protocol to ascertain if the protocol meets the definition of expedited status. The Chairperson indicates on IRBNet which category the protocol meets expedited status. If the protocol does not meet expedited status, the Chairperson brings the protocol to the convened IRB. A list of all approved expedited protocols are reviewed and included as informational items in the IRB minutes. Documentation for expedited reviews are maintained in IRBNet and include the category and circumstances that justify using expedited procedures. The investigator is notified in writing of the final decision. Approved expedited review satisfies the conditions (1) that it involves minimal risk, or (2) for a minor change.

Categories of Research That May be Reviewed by The Institutional Review Board (IRB) Through an Expedited Review Procedure:

Expedited Initial Review. The following criteria apply to all categories:

- The research presents no greater than minimal risks to subjects
- The research includes reasonable and appropriate protections so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal, if the identification of the participants or their responses will reasonably place them at risk of criminal or civil liability or be damaging to their financial standing, employability, insurability, reputation, or be stigmatizing.
- The research is not classified

- 1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met:
 - (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
 - (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR 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, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
 - (b) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.
- 3) Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a non-disfiguring 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 gumbase 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 non-research 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 at 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 HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

Convened Review. A convened review is utilized for research activities/protocols when they do not meet the criteria for either **exempt** or **expedited review**. The IRB conducts *initial* and *continuing reviews* of all non-exempt research at convened meetings at which a majority of the members are present, unless the research falls into one or more of the categories appropriate for *expedited review*. A majority of the IRB members, including at least one member whose primary concerns are in non-scientific areas must be present to conduct a convened meeting. For research to be approved, it must receive the approval of a majority of those members present at the meeting where a quorum is present. A quorum is met when a majority of the voting members are in attendance. When the IRB is not required to conduct continuing review, records must provide a rationale for any decisions to conduct continuing review of research otherwise eligible for review using the expedited procedure.

Continuing Review. The following criteria apply to continuing reviews:

- 1) Unless an IRB determines otherwise, continuing review of research is not required in the following circumstances:
 - i. Research eligible for expedited review as listed above (in accordance with §46.110);

- ii. Research reviewed by the IRB in accordance with the limited IRB review described in §46.104(d)(2)(iii), (d)(3)(i)(C), or (d)(7) or (8);
- iii. Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
 - (A) Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
 - (B) Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

Additional considerations for continuing review in multi-center trials monitored by DSMB, sponsors, or other similar monitoring boards. The IRB may rely on a current statement from a Data Safety Monitoring Board (DSMB) or sponsor indicating that it has reviewed study-wide adverse events, 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. The IRB will receive and review reports of local, on-site adverse events and unanticipated problems involving risks to subjects or others and any other information needed to ensure that its continuing review is substantive and meaningful.

Protocol changes or amendments can be reviewed through convened or expedited review. The changes or amendments can only be implemented after the investigator has received written notification of IRB approval. The IRB will determine what information must be conveyed to the human subjects. The investigator must communicate, in writing, any changes or amendments identified by the IRB to the human subject in a timely manner.

Criteria for Requiring Review More Often Than Annually. The IRB may require review more often than annually when any of the following are true:

- Procedures not before used in humans.
- More than minimal risk to vulnerable populations with no prospect of direct benefit.
- A high likelihood that participants will die due to the research procedures.
- Any other reason for which the IRB wants closer monitoring.

In specifying an approval period of less than 1 year, the IRB may define the period with either a time interval or a maximum number of subjects, (i.e., after 3 months or after three subjects). The IRB will determine the time interval or number of subject and the IRB minutes will clearly reflect these determinations regarding risk and approval period.

To Approve the Research Activity. To approve a research activity, the IRB must comply with the following regulatory criteria:

- 1) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:
 - (a) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design (including scientific or scholarly validity) 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.

- (b) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may 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 that 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.
 - (c) 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, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.
 - (d) 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 part 21 CFR §50.20, 21 CFR §46.116, and 38 CFR §16.116.
 - (e) Informed consent will be appropriately documented, in accordance with and to the extent required by 21 CFR §50.27, 21 CFR §46.117, and 38 CFR §16.117.
 - (f) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
 - (g) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- 2) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.
 - 3) In order to approve research in which some or all of the subjects are children, an IRB must determine that all research is in compliance with part 21 CFR §50, subpart D.

Outcomes of IRB Review. The IRB will notify investigators in writing of its determinations. The IRB actions, upon review of research, include the following:

- 1) Approved with no changes (or no additional changes). The research may proceed.

- 2) Modifications Required. Revisions to be reviewed by the IRB Chairperson or a designated IRB member. Such minor revisions must be clearly delineated by the IRB so the investigator may simply concur with the IRB's stipulations. These revisions should not include the use of words like "clarify", "explain" or "provide more information" since they are not specific and would require a judgment that the full board should make. The research may proceed **after** the required changes are verified and the protocol approved by the designated reviewer.
- 3) Modifications Required. Revisions to be reviewed at a convened IRB meeting. The research may proceed only after the convened IRB has reviewed and approved the required changes to the research.
- 4) Deferred pending receipt of additional substantive information. The IRB determines that it lacks sufficient information about the research to proceed with its review. The research may not proceed until the convened IRB has approved a revised application incorporating all necessary information.
- 5) Not Approved. The IRB has determined that the research cannot be conducted at the facility or by employees or agents of the facility.

Five Year Resubmission of All Research Activities. In addition to the annual Continuing Review, all research activities requiring continuing review will be subject to a total resubmission every five years to ensure compliance. Full-convened reviews will require an evaluation and review of all materials as performed in the initial review.

Expiration of Approval Period. The expiration date is the first day that the protocol is no longer approved. The expiration date is calculated as follows:

- If the research is approved by a convened IRB or approved with modifications (or conditions) with subsequent approval of responsive materials by the expedited procedure, the expiration date is the date of the convened IRB meeting plus the approval interval. (Example: If approved with modification by the convened IRB on 3/5/2017 for one year and granted final approval by the IRB chair on 3/19/2017, the expiration date is 3/5/2018.)
- If the research is approved by a convened IRB with modifications with subsequent approval of responsive materials by the convened IRB, the expiration date is the date of the last convened IRB meeting plus the approval interval. (Example: If approved with modifications by convened IRB on 3/5/2017 for one year and granted final approval by the convened IRB on 3/19/2017, the expiration date is 3/19/2018.)

The IRB approval period for research may extend no more than one year after the convened IRB meeting at which the research was last approved. The regulations permit **no grace period** to this 1-year requirement. Therefore, continuing review and re-approval of research must occur on or before the date when IRB approval expires. ORI recognizes the logistical advantages of keeping the IRB approval period constant from year to year throughout the life of each project. When continuing review occurs annually and the IRB performs continuing review within 30 days before the IRB

approval period expires, the IRB may retain the fixed anniversary date as the date by which the continuing review must occur.

Study Closure Due to Expiration. If a study expires on IRBNet a system generated email is sent to the principal investigator and co-investigator(s) stating that all study related activities (i.e. consenting, data collection, etc.) must cease. **To ensure the closure notification has been received and all study related activities have ceased, the principal investigator must provide written confirmation to the IRB Coordinator stating that all research activity has ceased.** A closure package will be generated by the IRB Coordinator and an expiration letter will be published on the IRBNet file. Once the written confirmation from the investigator is received it will be published under the Board Documents section of the IRBNet closure package generated by the IRB Coordinator. Until closure confirmation is received, no new studies will be processed for that principal investigator and active studies for that investigator are subject to suspension by the ORI Director if closure confirmation is not received within 10 days. Failure of the principal investigator to submit a closure letter within 10 days will be reported to the ORI Director for investigation of possible non-compliance.

Research that continues after the approval period expires is research conducted without IRB approval and the investigator will be subject to disciplinary action. Research that does not receive IRB continuing review and approval prior to the end of the stipulated approval period becomes expired. All research activities must stop, including recruitment, enrollment, interventions, interactions, and data analysis. If an investigator believes that currently enrolled participants will be harmed by stopping interventions, the investigator must provide a list of such participants and the reasons why participation in the research should continue. The IRB chair, and in the case of VA research the IRB chair in consultation with the VA Medical Director, will determine which participants may continue because of an over-riding safety concern or ethical issue involved such that it was in the best interests of individual participants to continue participating in the research interventions or interactions. Under no circumstances will investigators be allowed to enroll new participants into expired research.

For VAMC Research that has expired before the continuing review was completed the following is required:

- The biomedical IRB must notify investigators to immediately submit to the IRB Chair a list of participants for who stopping research activities would cause harm.
- The IRB Chair, with appropriate consultation with the MCD, determines within two business days whether subjects on the list may continue participating in the research interventions or interactions.
- Prompt reporting of the expiration to the sponsor if applicable.

Suspension or Termination of IRB Approval of Research. 45 CFR §46.113 states the following:

"An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head."

Any suspensions and terminations by someone other than the convened IRB must be reported to and reviewed by the convened IRB.

- 1) *Suspension of previously approved research.* Suspension of IRB approval: An action taken by the IRB to temporarily or permanently withdraw approval for some or all research activities short of permanently withdrawing approval for all research activities.
- 2) *Termination of previously approved research.* Termination of IRB approval: An action taken by the IRB to permanently withdraw approval for all research activities.

The IRB utilizes the following process to suspend or terminate previously approved research:

- 1) The IRB Chairperson is authorized to make suspension and termination determinations.
- 2) The IRB Chairperson will evaluate all possible suspensions and terminations on an urgent basis.
- 3) When a termination or suspension involves the withdrawal of current participants from the research:
 - (a) Enrolled participants will be notified;
 - (b) The withdrawal of enrolled participants must take into account their rights and welfare; and
 - (c) When follow-up of participants for safety reasons is permitted or required, participants will be so informed and any adverse events or unanticipated problems involving risks to participants or others will be reported to the IRB and others as required by the protocol and organizational policies and procedures.

It is the responsibility of the Director, ORI to provide prompt written notification to the Vice President for Research (Institutional Official) and regulatory agencies when:

- It has been determined that an incident of non-compliance is serious or continuing.
- It has been determined that an event is an unanticipated problem.
- The IRB suspends or terminates its approval of research.

The Director, ORI is also responsible for the reporting of:

- All events involving VA research to the VA Research and Development Office and the VA Office of Research Oversight.
- Unauthorized use, loss, or disclosure of individually identifiable information.
- Violations of information security requirements to the appropriate Information Security Officer.

Appeal of IRB Determinations. The IRB notifies the investigator in writing of its reason(s) for disapproving or requiring modifications. The investigator has the opportunity to respond in person or in writing after which the IRB must carefully and fairly evaluate the response in making the final

determination. The Director, ORI and the IRB Chair will meet to determine the most appropriate method of response, written or in person, taking into consideration the circumstances.

Conducting Sponsored Research. For sponsored research, the contracts and agreements with sponsors must include language that Marshall University will conduct sponsored research in accordance with the protocol/grant/contract, its policies and procedures and its ethical standards.

Contracts with sponsors should include language similar to:

- "The sponsor agrees to promptly notify the organization of any information discovered through the on-site monitoring process that could affect the safety of participants, affect the willingness of participants to continue participation, influence the conduct of the study, or alter the IRB's approval to continue the study."
- "The sponsor agrees to promptly notify the organization of any research study results that could affect the safety or medical care of current or former participant."

Contracts or other funding agreements require the sponsor to send data and safety monitoring plans and reports to Marshall University. Contracts or other funding agreements specify the time frame for providing routine and urgent data and safety monitoring reports to Marshall University as indicated in the data and safety monitoring plan approved by the IRB.

When Participant Safety Could be Directly Affected by Study Results after the Study has Ended.

Contracts or other funding agreements need to describe the steps followed to communicate findings from a closed (completed) research study to the investigator or Marshall University when those findings directly affect subject safety. These contracts or other funding agreements should specify a time frame after study closure during which the sponsor will communicate such findings. The time frame for this must be appropriate to the study but should at least be two years or upon completion of data analysis.

Grant and Contract Compliance. Contracts from the Grant and Contract Compliance Office should include language that:

- Requires the organization to comply with the protocol, applicable law, and its ethical standards.
- Describes who takes responsibility to provide and pay for medical care for research-related injury.
- If the sponsor has a regulatory obligation to monitor the conduct of the research, contracts must include language that obligates the sponsor to promptly notify the organization of any information discovered through the monitoring process that could affect the safety of participants, affect the willingness of participants to continue participation, influence the conduct of the study, or alter the IRB's approval to continue the study.
- Requires the sponsor to comply with the organization's policies and procedures regarding the publication of findings from sponsored research.
- If the results of the research directly affect the safety or medical care of current or former participants, the sponsor is required to notify the organization of those results.

A federally funded grant application or proposal involving human subject research is not required to be submitted with the IRB application for IRB review. However, keep in mind that no funding can be distributed until the IRB has reviewed and approved the study. 45CFR46.103(d) states:

..." Certification is required when the research is supported by a Federal department or agency and not otherwise waived under §46.101(i) or exempted under §46.104. For such research, institutions shall certify that each proposed research study covered by the assurance and this section has been reviewed and approved by the IRB. Such certification must be submitted as prescribed by the Federal department or agency component supporting the research. Under no condition shall research covered by this section be initiated prior to receipt of the certification that the research has been reviewed and approved by the IRB...."

Monetary Fees for IRB Reviews. If the full convened or expedited protocol is industry sponsored, the ORI will be charging the sponsor a one time fee of \$2,500 that will cover the initial review and all continuing IRB reviews. The fee is the same for industry sponsored expedited reviews. Payment is to be made to the Marshall University Research Corporation and must be paid prior to IRB review.

Waivers of Fees. There may be extenuating circumstances where such a charge would be unwarranted (e.g., small project budgets). Please contact the Director ORI with requests for waiver of the IRB fee.

Research in Foreign Countries. When it becomes necessary to conduct research in a foreign country certain precautions must be taken. It is important to be cognizant and respectful of the laws and customs of that country. In order for the IRB to make a complete evaluation of a research proposal to be conducted in a foreign country the investigator must be able to explain the laws and customs of that area. Therefore, the investigator is required to supply the IRB with documented permission from local authorities or ethic committees to conduct the research. If the region does not contain such authority then an explanation of the laws and customs of the area must be submitted.

When Following DOD Requirements for Research in Foreign Countries. The DoD Component must conduct an appropriate administrative review of the research involving human subjects. The DoD Component administrative review must be conducted before the research involving human subjects can begin, to ensure compliance with all applicable regulations and policies, including any applicable laws and requirements and cultural sensitivities of the country when the research is conducted in a country other than the United States.

When Following VA Requirements for Research in Foreign Countries:

- The Medical Center Director (MCD) must ensure all international research is approved explicitly in a document signed by the MCD, except for Cooperative Studies Program activities which must be approved by the CRADO.
- All international sites must hold an international Federalwide assurance, and the research must be approved by the IRB or Ethics Committee of the participating sites listed on the international Federalwide assurance.

- International research includes VA-approved research conducted at international sites not within the United States, its territories, or Commonwealths; and includes research where human tissues are sent outside the United States.
- The investigator must conduct the research in accordance with VA requirements and all other applicable federal requirements for protecting human subjects, tissue banking, use of databases, federal criminal laws, and the standards of ethical conduct for employees of the executive branch.

Chapter 25 - Vulnerable Subjects

PURPOSE: To ensure that potentially vulnerable subject groups are equitably recruited, selected, and protected during research activities.

POLICY: To give special consideration to protecting the welfare of vulnerable subjects, such as children, prisoners, pregnant women, mentally disabled persons, economically, or educationally disadvantaged persons.

SCOPE: This policy covers all human subjects that are or may be considered potentially vulnerable subjects, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons who may potentially be enrolled in research activities.

DEFINITIONS:

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

Assent means a child's oral or written affirmative agreement to participate in research. Every effort should be made to obtain assent even in small children, (i.e., 3 years of age or younger) and mere failure to object should not, absent affirmative agreement, be construed as assent. Assent is documented in children who are 7 years of age or older unless the IRB has determined otherwise.

Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research.

Parent means a child's biological or adoptive parent.

Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child.

Prisoner is an 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 which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial or sentencing.

RESPONSIBILITIES:

IRB Chairperson and members are responsible for ensuring that the rights and welfare of research subjects are protected. They are responsible for ensuring recruitment and selection of human subjects

is performed in a manner free from coercion and undue influence. The IRB is responsible for ensuring that the informed consent contains information sufficient for the subject to assess risks and benefits and that the language utilized is at the vulnerable subject's level of understanding. The IRB must ensure that it has adequate representation on the Board to consider specific kinds of research involving these vulnerable populations in a competent manner. The IRB must carefully consider group characteristics, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable subjects.

Principal Investigator (PI) is responsible for ensuring that all vulnerable human subjects are protected and participate voluntarily in an environment free from coercion or undue influence. The PI has the responsibility to ensure the informed consent has sufficient information about the research and its risks and benefits for the subject to reach an informed decision as to whether they will voluntarily participate and that the subject understands the informed consent. The investigator is responsible for explaining to the subject his/her rights including the protection of the subject's privacy and confidentiality of information.

PROCEDURES:

IRB Considerations. The IRB carefully considers the following specific elements of the research plan when reviewing research involving vulnerable subjects:

- 1) Strategic issues include inclusion and exclusion criteria for selecting and recruiting subjects; informed consent and willingness to volunteer; coercion and undue influence; and confidentiality of data.
- 2) Group characteristics, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable subjects.
- 3) Investigators are not permitted to over-select or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research subjects merely because they are a readily available "captive" population.
- 4) The IRB is knowledgeable about applicable state or local laws that bear on the decision-making abilities of potentially vulnerable populations. State statutes often address issues related to competency to consent for research, emancipated minors, legally authorized representatives, the age of majority for research consent, and the waiver of parental permission for research.
- 5) Research studies that plan to involve any potentially vulnerable populations must have adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and informed consent or assent. When weighing the decision whether to approve or disapprove research involving vulnerable subjects, the IRB ensures and requires that such procedures are a part of the research plan. It may be possible for researchers to enhance the understanding for potentially vulnerable subjects. Examples include, having someone not involved in the research to obtain the consent, the inclusion of a consent monitor, a subject advocate,

interpreter for hearing-impaired subjects, translation of informed consent forms into languages the subjects understand, and reading the consent form to subjects slowly and ensuring their understanding paragraph by paragraph.

- 6) The IRB may require additional safeguards to protect potentially vulnerable populations. For instance, the IRB may require that the investigator submit each signed informed consent form to the IRB, that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.
- 7) If research involves adults unable to consent, the IRB considers specific criteria for approval of such research that provides additional safeguards to protect their rights and welfare.

When following Department of Defense (DoD) regulations the following applies:

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

When following Department of Education regulations there must be a description of:

- 1) The process to comply with the Protection of Pupil Rights Amendment:
 - (a) For research funded by the U.S. Department of Education: No student shall be required, as part of any research project, to submit without prior consent to surveys, psychiatric examination, testing, or treatment, or psychological examination, testing, or treatment, in which the primary purpose is to reveal information concerning one or more of the following:
 - i. Political affiliations.
 - ii. Mental and psychological problems potentially embarrassing to the student or his or her family.
 - iii. Sex behavior and attitudes.
 - iv. Illegal, anti-social, self-incriminating and demeaning behavior.
 - v. Critical appraisals of other individuals with whom the student has close family relationships.
 - vi. Legally recognized privileged and analogous relationships, such as those of lawyers, physicians, and ministers.
 - vii. Religious practices, affiliations, or beliefs of the student or student's parent.
 - viii. Income, other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under a program.
- 2) Prior consent means:
 - (a) Prior consent of the student, if the student is an adult or emancipated minor; or

- (b) Prior written consent of the parent or guardian, if the student is an un-emancipated minor. Schools and contractors obtain prior written parental consent before minor students are required to participate in any ED-funded survey, analysis, or evaluation.
- 3) For research not funded by the US Department of Education: The IRB must verify compliance with U.S. Department of Education regulations that schools are required to develop and adopt policies in conjunction with parents regarding the following:
 - (a) The right of a parent of a student to inspect, upon the request of the parent, a survey created by a third party before the survey is administered or distributed by a school to a student.
 - (b) Any applicable procedures for granting a request by a parent for reasonable access to such survey within a reasonable period of time after the request is received.
 - (c) Arrangements to protect student privacy that are provided by the agency in the event of the administration or distribution of a survey to a student containing one or more of the following items (including the right of a parent of a student to inspect, upon the request of the parent, any survey containing one or more of such items):
 - i. Political affiliations or beliefs of the student or the student's parent.
 - ii. Mental or psychological problems of the student or the student's family.
 - iii. Sex behavior or attitudes.
 - iv. Illegal, anti-social, self-incriminating, or demeaning behavior.
 - v. Critical appraisals of other individuals with whom respondents have close family relationships.
 - vi. Legally recognized privileged or analogous relationships, such as those of lawyers, physicians, and ministers.
 - vii. Religious practices, affiliations, or beliefs of the student or the student's parent.
 - viii. Income (other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under such program).
 - (d) The right of a parent of a student to inspect, upon the request of the parent, any instructional material used as part of the educational curriculum for the student.
 - (e) Any applicable procedures for granting a request by a parent for reasonable access to instructional material received.
 - (f) The administration of physical examinations or screenings that the school or agency may administer to a student.
 - (g) The collection, disclosure, or use of personal information collected from students for the purpose of marketing or for selling that information (or otherwise providing that information to others for that purpose), including arrangements to protect student

privacy that are provided by the agency in the event of such collection, disclosure, or use.

- (h) The right of a parent of a student to inspect, upon the request of the parent, any instrument used in the collection of personal information before the instrument is administered or distributed to a student.
- (i) Any applicable procedures for granting a request by a parent for reasonable access to such instrument within a reasonable period of time after the request is received.

Pregnant Women, Human Fetuses, and Neonates. For additional information concerning this topic refer to the Code of Federal Regulations (45 CFR 46 Subpart B). If a study involves pregnant women, fetuses and neonates then the investigator must submit the Pregnant Women Checklist in addition to the other required IRB documents. This checklist can be located in the IRBNet library and on the ORI website.

For research involving pregnant women, human fetuses, and neonates:

- 1) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, has been conducted and provide data for assessing potential risks to pregnant women and fetuses.
- 2) One of the following is true:
 - (a) 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.
 - (b) 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) For children who are pregnant, assent and permission are obtained in accordance with the regulations.
- 5) No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
- 6) Individuals engaged in the research have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
- 7) Individuals engaged in the research have no part in determining the viability of a neonate.
- 8) Where scientifically appropriate, preclinical and clinical studies has been conducted and provided data for assessing potential risks to neonates.

9) Individuals engaged in the research have no part in determining the viability of a neonate.

10) One of the following is true:

- (a) The research held 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.
- (b) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there is no added risk to the neonate resulting from the research.

The IRB determines whether the approval criteria for consent and permission are met when research involves pregnant women or fetuses. The IRB Chair will have the IRB determine and document that:

- 1) The consent of the mother is obtained in accordance with the regulations.
- 2) If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the father is also obtained in accordance with the regulations, except that the father's consent does not need to be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
- 3) Individuals providing consent are fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.

The IRB determines whether the criteria for approval of research are met when research involves nonviable neonates. The IRB Chair will have the IRB determine and document that:

- 1) Where scientifically appropriate, preclinical and clinical studies has been conducted and provided data for assessing potential risks to neonates.
- 2) Individuals engaged in the research have no part in determining the viability of a neonate.
- 3) Vital functions of the neonate are not artificially maintained.
- 4) The research will not terminate the heartbeat or respiration of the neonate.
- 5) There is no added risk to the neonate resulting from the research.
- 6) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.

The IRB determines whether the approval criteria for consent and permission are met when research involves neonates of uncertain viability. The IRB Chair will have the IRB determine and document that:

- 1) Individuals providing consent are fully informed regarding the reasonably foreseeable impact of the research on the neonate.
- 2) The legally effective consent of either parent of the neonate is obtained in accordance with the regulations.
 - (a) If neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective consent of either parent's legally authorized representative is obtained.
 - (b) The consent of the father or his legally authorized representative does not have to be obtained if the pregnancy resulted from rape or incest.

The IRB determines whether the approval criteria for consent and permission are met when research involves nonviable neonates. The IRB Chair will have IRB determine and document that:

- 1) Individuals providing consent are fully informed regarding the reasonably foreseeable impact of the research on the neonate.
- 2) The legally effective consent of both parents of the neonate is obtained in accordance with the regulations.
 - (a) If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the consent of one parent of a nonviable neonate is sufficient, except that the consent of the father does not have to be obtained if the pregnancy resulted from rape or incest.
 - (b) The consent of a legally authorized representative of either or both of the parents of a nonviable neonate is not allowed.
- 3) The waiver and alteration provisions are not applied.

When following DHHS regulations the following applies:

- 1) When research involves pregnant women, the IRB determines that the consent of the pregnant women is required if the research holds out:
 - (a) The prospect of direct benefit to the pregnant woman.
 - (b) The prospect of direct benefit both to the pregnant woman and the fetus.

- (c) No prospect of benefit for the woman or 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.
- 2) When research involves pregnant women, the IRB determines that the consent of the pregnant woman and the father is required, 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 if the research holds out the prospect of direct benefit solely to the fetus.
- 3) When the research involves neonates of uncertain viability, the IRB determines that the consent of either parent of the neonate is required or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective consent of either parent's legally authorized representative is required, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.
- 4) When the research involves non-viable neonates, the IRB determines that the consent of both parents is required, except:
 - (a) If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the consent of one parent is required.
 - (b) If the pregnancy resulted from rape or incest the consent of the father need not be obtained.
- 5) When the research involves non-viable neonates, the IRB is not allowed to approve the consent of a legally authorized representative.

Research Involving Prisoners. For additional information concerning this topic refer to the Code of Federal Regulations (45 CFR 46 Subpart C). The IRB will utilize the prison study review question sheet located in the IRBNet library to ensure all federal requirements are met.

For the review of research involving prisoners:

- 1) A majority of the IRB (exclusive of prisoner members) have no association with the prison involved, apart from their membership on the IRB.
- 2) At least one IRB member who is a prisoner or a prisoner representative with appropriate background and experience to serve in that capacity is present at the meeting.
- 3) For prisoners, "minimal risk" means the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

The IRB determines whether the criteria for approval of research are met when research involves prisoners. The IRB determines and documents that:

- 1) The research represents one of the following categories:
 - (a) 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.
 - (b) 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.
 - (c) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults).
 - i. For DHHS-funded research, OHRP has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of its intent to approve such research.
 - (d) Research on practices, both innovative and accepted that has the intent and reasonable probability of improving the health or well-being of the subject.
 - i. For DHHS-funded research which require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after OHRP has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of its intent to approve such research.
 - (e) Epidemiologic studies that meet the following criteria:
 - i. The sole purposes are one of the following:
 - (1) To describe the prevalence or incidence of a disease by identifying all cases.
 - (2) To study potential risk factor associations for a disease.
 - ii. The research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
 - iii. Prisoners are not a particular focus of the research.
- 2) 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.

- 3) The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.
- 4) Procedures for the selection of participants within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners.
- 5) Unless the principal investigator provides justification in writing for following some other procedures, control participants are selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.
- 6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole.
- 7) When there is a need for follow-up examination or care of participants after the end of their participation, adequate provisions are made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.
- 8) For DHHS-funded research, indicate the individual (by title of position) who certifies to OHRP the duties of the IRB have been fulfilled.

For research involving prisoners reviewed by the convened IRB:

- 1) 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.
- 2) The prisoner representative must review research involving prisoners, focusing on the requirements in Subpart C or equivalent protections. 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) 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.

- 6) 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).
- 7) 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).

For research involving interaction with prisoners reviewed by the expedited procedure:

- 1) 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.
- 2) 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.
- 3) 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.

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

- 1) Research that does not involve 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.
- 2) Review by a prisoner representative is not required.
- 3) The prisoner representative may review the research as a reviewer or consultant if designated by the IRB chair.
- 4) Review of modifications and continuing review must use the same procedures as initial review.

The Exempt procedure cannot be used for research involving prisoners.

If a subject becomes a prisoner while enrolled in a research study that was not reviewed according to Subpart C:

- When Subpart C applies:
 - Terminate enrollment or review the research study under Subpart C if it feasible for the subject to remain in the study.
 - Before terminating the enrollment of the incarcerated subject, the IRB should consider the risks associated with terminating participation in the study.
 - If the subject cannot be terminated for health or safety reasons:
 - Keep the subject 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 subject to remain in the study, keep the subject enrolled and inform OHRP of the decision along with the justification.
- Remove the subject from the study and keep the subject on the study intervention under an alternate mechanism such as compassionate use, off label use, etc.

Note: If a participant is incarcerated temporarily while enrolled in a study:

- If the temporary incarceration has no effect on the study, keep the participant enrolled.
- If the temporary incarceration has an effect on the study, handle according to the above guidance.

Research Involving Children. For additional information concerning this topic refer to the Code of Federal Regulations (45 CFR 46 Subpart D).

The IRB determines whether the criteria for approval of research are met when research involves children. The IRB Chair will have the IRB determine and document that:

- Category 1:
 - No greater than minimal risk to children is presented
- Category 2:
 - More than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual participant, or by a monitoring procedure that is likely to contribute to the participant's well-being.
 - The risk is justified by the anticipated benefit to the participants.
 - The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches.
- Category 3:
 - More than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual participant, or by a monitoring procedure which is not likely to contribute to the well-being of the participant.
 - The risk represents a minor increase over minimal risk.
 - The intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations.
 - The intervention or procedure is likely to yield generalizable knowledge about the participants' disorder or condition which is of vital importance for the understanding or amelioration of the participants' disorder or condition.
- Category 4:
 - 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 federal agency, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determined either:
 - That the research fell into categories 1 through 3; or
 - The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children and the research will be conducted in accordance with sound ethical principles.

The IRB determines whether the criteria for approval of research are met when research in Category 3 or 4 involves wards of the state or any other agency. The IRB Chair will have the IRB determine and document that:

- The research is:
 - Related to their status as wards; or
 - Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involves as subjects are not wards.
- The IRB requires appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis.
 - The advocate is 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.
 - The advocate is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigators, or the guardian.

When following DHHS or FDA regulations involving children the following applies:

- The IRB must follow the requirements in Subpart D pertaining to obtaining assent of children and permission of the parents or guardian.
- For research that involves no more than minimal risk or more than minimal risk with the prospect of direct benefit to the individual children, the IRB determines whether:
 - The permission of both parents is required unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child, or the permission of one parent is sufficient.
 - For research that involves more than minimal risk without the prospect of direct benefit to the individual children, the IRB determines that the permission of both parents is required unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
- The IRB determines and documents that assent is a requirement of:
 - All children.
 - Some children.
 - None of the children.
- When the IRB determines that assent is not a requirement of some children, the IRB determines and documents which children are not required to assent.
- When the IRB determines that assent is not a requirement for some or all children, the IRB determines and documents one or more of the following:

- The children are not capable of providing assent based on the age, maturity, or psychological state.
- The capability of the children is so limited that they cannot reasonably be consulted.
- The intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the child and is available only in the context of the research.
- Assent can be waived using the criteria for waiver of the consent process.
- When the IRB determines that assent is a requirement, the IRB determines whether:
 - Assent will be documented.
 - If so, the process to document assent.

Research Involving Other Potentially Vulnerable Adult Subjects. Employees, students, and trainees at Marshall University also may be considered vulnerable subjects. Thus, the IRB upholds the same standards in approving research involving these groups as other vulnerable subject research. The context of the research is an important consideration for the IRB to have in mind when reviewing research that involves other potentially vulnerable subjects. Research involving homeless persons, members of particular minority groups, or the economically or educationally disadvantaged pose significant challenges. Research involving significant follow-up procedures or offering significant monetary compensation may unduly influence certain types of subjects, and the IRB must take such considerations into account. Nevertheless, research involving these subjects is socially important for understanding and eventually improving adverse health in these populations. When some or all of the participants are likely to be vulnerable additional safeguards must be included in the protocol to protect their rights and welfare. For example, if a participant regained decision-making capacity then the investigator should consider repeating the consent process with the participant, and obtain the participant's permission to continue with the study.

When a research study involves populations with diminished decision-making capacity not covered by specific policies and procedures, describe, in general, the steps followed by the IRB to evaluate the consent process for these populations.

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

- The proposed plan for the assessment of the capacity to consent is adequate.
- Assent of the subjects is a requirement, and, if so, whether the plan for assent is adequate.
- The IRB determines and documents that assent is a requirement.

Research Involving Deceased Persons. Research involving deceased persons is not covered by the FDA human subject regulations or the Common Rule.

Department of Defense Regulated Research. When following DoD regulations the following applies for research involving pregnant women, prisoners and children:

- Research involving pregnant women, prisoners, and children are subject to the DHHS Subparts B, C. and D.

- For purposes of applying Subpart B, the phrase “biomedical knowledge” shall be replaced with “generalizable knowledge.”
- The applicability of Subpart B is limited to research involving pregnant women as participants in research that is more than minimal risk and included interventions or invasive procedures to the woman or the fetus or involving fetuses or neonates as participants.
- Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.
- Research involving prisoners cannot be reviewed by the expedited procedure.
- When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum.
- In addition to allowable categories of research on prisoners in Subpart C, epidemiological research is also allowable when:
 - The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.
 - The research presents no more than minimal risk.
 - The research presents no more than an inconvenience to the participant.
- If a participant becomes a prisoner, if the researcher asserts to the IRB that it is in the best interest of the prisoner-participant to continue to participate in the research while a prisoner, the IRB chair may determine that the prisoner-participant may continue to participate until the convened IRB can review this request to approve a change in the research protocol and until the organizational official and DoD Component office review the IRB’s approval to change the research protocol. Otherwise, the IRB chair shall require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened IRB can review this request to approve a change in the research protocol. The convened IRB, upon receipt of notification that a previously enrolled human participant has become a prisoner, shall promptly re-review the research protocol to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert having the expertise of a prisoner representative if the IRB reviewing the research protocol does not have a prisoner representative. If the prisoner-participant can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-participant’s confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human participants from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-participant to continue to participate in the research. This approval is limited to the individual prisoner-participant and does not allow recruitment of prisoners as participants.
 - Research involving a detainee as a human participant is prohibited.
 - This prohibition does not apply to research involving investigational drugs and devises when the same products would be offered to US military personnel in the same location for the same condition.
- Research involving children cannot be exempt.
- Research involving prisoners of war is prohibited.
- The IRB is aware of the definition of “prisoner of war” for the DoD component granting the addendum.

VAMC Research. For VA research involving:

- Fetuses cannot be approved.
- In vitro fertilization cannot be approved.
- Prisoners as participants cannot be approved unless a waiver has been granted by the Chief Research and Development Officer. (VHA Directive 1200.05, paragraph 20)
- Children as participants cannot be approved unless criteria set forth by the VA in the VHA Handbook 1200.05. (VHA Directive 1200.05, paragraph 21)
- Pregnant women as participants cannot be approved unless the additional VA criteria is met in VHA Directive 1200.05. (VHA Directive 1200.05, paragraph 19)
- Research involving stem cells shall be governed by the policy set by NIH.
- VA investigators cannot conduct interventions in neonates by VA investigators while on official duty, or at VA facilities, or at VA-approved off-site facilities. Prospective observational or retrospective record review studies that involve neonates or neonatal outcomes are permitted.
- Biological specimens and data obtained from children is considered research involving children even if de-identified.
- Research involving adults who are unable to consent may occur only when the IRB determines the proposed research:
 - Does not present greater than minimal risk, or
 - Presents a greater probability of direct benefit to the subject than harm to the subject, or
 - Poses greater than minimal risk and no prospect of direct benefit to individual subjects but is likely to yield generalizable knowledge about the subject's disorder or condition that is of vital importance to understanding or amelioration of the subject's disorder or condition.
 - In addition, the IRB determines the research cannot be performed solely on adults who can consent, and the focus of the research is the disorder leading to the lack of decision-making capacity, or
 - Where the subject of the research is not directly related to the subject's lack of decision-making capacity, the investigator has presented a compelling reason for including adults unable to consent.
- The research protocol must address how the investigator will assess capacity and determine when surrogate consent is required.
- Consent is limited by a legally authorized representative to situations where the prospective subject 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.
- Consent from the legally authorized representative of the subject can only be obtained from the following: a healthcare agent (i.e., an individual named by an individual in a durable power of attorney for health care); legal guardian or special guardian; next of kin in this order: a close relative of the patient 18 years of age or older, in the following priority: spouse, child, parent, sibling, grandparent, or grandchild; or close friend, unless otherwise specified by applicable state law.
- If there is any question as to whether a potential adult subject has decision-making capacity, and there is no documentation in the medical record that the individual lacks decision-making capacity, and the individual has not been ruled incompetent by a court of law, the investigator

must consult with a qualified practitioner (who may be a member of the research team) about the individual's decision-making capacity before proceeding with the consent process.

- Individuals, who because of a known condition, are at high risk to temporary or fluctuating lack of decision-making capacity must be evaluated by a qualified practitioner to determine the individual's ability to provide consent. This evaluation must be performed as described in the IRB-approved protocol.
- If the individual is deemed to lack decision-making capacity at the time of their participation in the study, a legally authorized representative must provide consent.
- If the subject regains decision-making capacity, the investigator must repeat the consent process with the subject and obtain the subject's permission to continue with the study.
- Disclosures to be made to the subject must be made to the subject's legally authorized representative.
- The subject's legally authorized representative must be told that that his or her obligation is to try to determine what the subject would do if able to make an informed decision. If the prospective subject's wishes cannot be determined, the legally authorized representative must be told that he or she is responsible for determining what is in the subject's best interest.
- Have the investigator explain the proposed research to the prospective subject when feasible even when the subject's legally authorized representative gives consent.
- Have the practitioner explain the proposed research to the prospective subject when feasible.
- Ensure the study includes appropriate procedures for respecting dissent. Prohibit subjects from being forced or coerced to participate in a research study.
- International research is not initiated unless permission is obtained from the MCD.

When following the ICH-GCP (E6)(R2) guidelines. When adults are unable to consent, the IRB determines:

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

Chapter 26 - Student Class Project Guidelines

PURPOSE: To ensure ethical conduct of research projects that are assigned as part of class projects.

POLICY: To ensure ethical conduct of research projects, instructors and faculty who assign class projects involving individuals as research subjects are expected to review students' plans prior to subject recruitment and data collection. Also any in-class presentation should be reviewed by the instructor prior to the actual student presentation to ensure that there is nothing that could be deemed offensive.

TRAINING: Instructors and students conducting research projects are required to complete the CITI training. The Office of Research Integrity can provide instructions for course registration, however the instructor must ensure that a course completion certificate has been received for each student.

CRITERIA: Research qualifies for the designation of student class project if:

- It is an activity designed as part of a course requirement for purposes of learning research methods and;
- The results and data will not be presented, posted, or published outside of the classroom.

A student class project does not meet the definition of human subject research if it is intended only for classroom purposes. The student cannot use the project for any presentation, conference, publication, thesis, dissertation, capstone project, or report outside of the course for which it is assigned.

The student must submit an IRB application if they intend to use the project outside of the classroom. This application must be approved before the student starts the project. Instructors should make this clear to their students.

CONSENT: Obtaining consent is important to the ethical conduct of research. It is required that students obtain consent from participants in their research projects. It is better to provide the students with a consent template to assist them in the creation of an informed consent document that will protect participants. A template will give the students experience in modifying the form to reflect the purpose of their particular study. The Office of Research Integrity (ORI) is available to assist with the development or approval of a consent template, though ORI approval is not required. Students may use a verbal script in certain circumstances (e.g., phone interview) to consent participants. If students will use verbal scripts instead of consent forms, instructors should make sure that their scripts are submitted for approval and accurately reflect the plans of the project.

RED FLAGS: The following are some red flags that the instructor should be aware of:

- The student expresses intent to use the project for a presentation, conference, publication, thesis, capstone project, or dissertation (they must submit an IRB application).

- The project's activities expose participants to more than "minimal risk" (minimal risk means no more risk than everyday life).
- The project involves sensitive/private information such as sexual attitudes or behaviors, illegal behaviors, and/or the use of alcohol or drugs.
- The project uses vulnerable populations (e.g., children under the age of 18, institutionalized persons, prisoners, persons who are "decisionally" impaired, etc.).
- Results of the project activities or data collected are recorded in such a way that the subjects are identifiable (images in videotapes or photographs and voices on audiotape are identifiable).
- There is no informed consent process in place.
- Subjects are under the direction or supervision of students collecting data (e.g. GAs collecting data from their own students or supervisors collecting data from employees).
- Students do not plan to maintain confidentiality of the data (e.g. using subjects' real names, inability to store consent forms in locked office/cabinet, etc.).
- Subjects are forced to participate or are ostracized if they do not participate.

HELPFUL TIPS: Here are some tips to help the instructors:

- The IRB is most concerned with protection of human subjects and their data. Thus a student project should be detailed in describing: source of subjects, recruitment methods of subjects, interaction with subjects, informed consent processes, maintaining confidentiality of data, and data storage. These areas of the project, if executed well, will ensure better protections.
- The IRB does have an abstract template that is available for use. The template can be modified to meet your individual needs.
- Interview guides that are not solidified can be submitted as "semi-structured" and updated later with approval prior to use. Any changes to a survey should be approved prior to use.
- An instructor who expects students to use the class project toward a publication or presentation outside of the classroom (thus needing IRB approval) may assist students by having them work in pairs, or by creating strict parameters for the class so that the project can be submitted under one application where the instructor is PI and the students are listed as co-investigators.