

# Investigator's Handbook



For the  
Protection of Human Participants  
In  
Social/Behavioral Research  
And  
Biomedical Research



**East Tennessee State University Institutional Review Board**  
**PO BOX 70565, Johnson City, TN 37614**  
**Phone 423- 439-6053 fax 423 - 439- 6060**  
**Website: [www.etsu.edu/irb](http://www.etsu.edu/irb)**

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## Foreword

This handbook is to help the investigator comply with the following concerning humans in research:

- ⇒ ETSU Institutional Policies
- ⇒ Institutional Review Board (IRB) Policies and Procedures
- ⇒ Federal Regulations
- ⇒ Ethical Principles
- ⇒ VA Policies and Procedures (if VA research)

Included in this handbook are:

- ⇒ Detailed information concerning Federal and Institutional requirements for the protection of human Subjects
- ⇒ Purpose of the IRB
- ⇒ Criteria for IRB Approval
- ⇒ Requirements and procedures for Initial and Continuing Review for the different levels and approval of research
- ⇒ Responsibilities of investigators during review and conduct of research
- ⇒ Requirements and procedures of notifying the IRB of unanticipated problems involving risks to subjects or others
- ⇒ Informed Consent Requirements
- ⇒ Issues on Vulnerable Populations
- ⇒ Requirements for the use of Investigational Devices (IDE) and investigational Drugs (IND)
- ⇒ Requirements on Amendments
- ⇒ Other Pertinent Information

Every effort have been made to assure all information in this handbook is consistent with all applicable Federal and State Laws and regulations, and with ETSU policies concerning the use of humans in research. As changes in laws and policies occur, this handbook will be revised.

## How to Use This Handbook

This handbook should give the investigator a better understanding on how to successfully submit a proposal to the IRB. It also gives the investigator an understanding of the guiding principles to protect humans participating in research.

The Table of Contents has a listing of the topics covered within this handbook. This will save time in looking for specific guidance.

Each chapter addresses specific issues pertinent to the investigators who are engaged in social/behavioral and/or biomedical research at East Tennessee State University and the James H. Quillen Veterans Affairs Medical Center. Chapters 1-10 & 13 relate to Social/Behavioral research and chapters 1-13 relate to Biomedical research.

It is crucial that you, the investigator, have an understanding of the ethical principles, the Federal regulations and the Institutional and IRB policies and procedures regarding research with humans.

## CHAPTER 1—Purpose and History of the Institutional Review

### INTRODUCTION

It is the policy of \*East Tennessee State University (ETSU) and the James H. Quillen Veterans Affairs Medical Center (VAMC) at Mountain Home (Johnson City), Tennessee to comply with all applicable local, state, federal, and international Good Clinical Practice (GCP) regulations in the conduct of human subject research. Written procedures are required to document the management of assurances of compliance. In accordance with the Federal Policy on the Protection of Human Subjects (Department of Health and Human Services [DHHS] Title 45, Code of Federal Regulations (CFR), Part 46, Food and Drug Administration (FDA) Title 21 CFR Parts 50 and 56, 38 CFR 16), ETSU and the VAMC are jointly responsible for the protection of the rights and welfare of human subjects of research conducted by, or under the supervision of physicians, faculty, staff, or students. To conduct this responsibility effectively, the University maintains Institutional Review Boards (IRB) to review research protocols involving human subjects and to evaluate both risk and protection against risk for those subjects. It is the function of the IRBs to 1) determine and certify that all research projects conducted by ETSU or by the VAMC, or by physicians, faculty, staff, or students of either institution, or for any institution for whom these services are provided by contractual agreement, conform to the regulations and policies set forth by the DHHS, Office for Human Research Protection (OHRP), the FDA, and other federal entities regarding the health, welfare, safety, rights, and privileges of human subjects; and 2) assist the investigator in complying with federal and state regulations.

\*Two Boards have been constituted within the Human Research Protection Program (HRPP) at East Tennessee State University to operate within the regulatory requirements of 45 CFR 46.107. These boards address the needs of both the ETSU research community and that of the James H. Quillen Veterans Affairs Medical Center (VAMC). Institutional responsibility is clarified and applicable throughout this document as follows:

### PARTICIPANTS

One Institutional Review Board (IRB) serves the academic campus of ETSU and is designated as the East Tennessee State University Campus IRB (ETSU IRB). Its members primarily hold terminal degrees such as the Ph.D. or Ed.D. degree and are drawn from the Colleges other than the Quillen College of Medicine, Per ETSU policy, the ETSU IRB will include at least nine voting faculty representatives as follows: one representative from the College of Business and Technology, one representative from the College of Clinical and Rehabilitative Health Sciences; one representative from the College of Nursing, one representative from the College of Public Health; one representing the humanities; one representing the social sciences within the College of Arts and Sciences; one representing the area of human development; one representing the areas of curriculum and instruction and educational leadership within the College of Education, and one representing the Faculty Senate. Staff and community representatives and one M.D. are included in its membership. The expertise is primarily in the social and behavioral sciences and in educational research. The ETSU IRB reviews non-medical research conducted by, or under the supervision of faculty, staff, or students of the institution. ETSU is responsible for the protection of the rights and welfare of human subjects engaged in the research activities reviewed for approval by this IRB. The participating institutions in the second Board, designated as the Medical Campus ETSU/VA IRB,

are East Tennessee State University and the James H. Quillen Veterans Affairs Medical Center. The second IRB serves the Quillen College of Medicine, the James H. Quillen VA Medical Center, and is also the IRB of record for Mountain States Health Alliance, a local hospital group. Its members are largely drawn from the Quillen College of Medicine and the James H. Quillen VAMC and hold either the M.D. or other doctoral degrees. Community members are included. Its expertise is in the medical sciences and clinical research. The Medical Campus East Tennessee State University/James H. Quillen Veterans Affairs Medical Center IRB (ETSU/VA IRB) reviews medical research conducted by, or under the supervision of physicians, faculty, staff, or students of either/both institutions. Research protocols submitted under contractual agreements from physicians and/or staff employed by any Mountain States Health Alliance (MSHA) institution are additionally reviewed for approval by the ETSU/VA IRB. East Tennessee State University (ETSU) and the James H. Quillen Veterans Affairs Medical Center (VA) at Mountain Home (Johnson City), Tennessee, are jointly responsible for the protection of the rights and welfare of human subjects engaged in the research activities reviewed for approval by this IRB.

The Institutional Review Board Administration, located on the campus of East Tennessee State University, serves as the official Human Research Protections Program (HRPP) provider for the James H. Quillen Veterans Affairs Medical Center. The HRPP is officially outlined and documented in the Policies and Procedures, the Memorandum of Understanding (MOU), and the OHRP approved Federal-wide Assurance. All policies are reviewed by both institutions and updated as necessary by the IRB.

Whether a study is reviewed by one board or the other depends upon the type of research, not just the College in which the investigators hold an appointment. For example, a study in exercise physiology would be reviewed by the Medical IRB if it involved evaluation of the effects of natural product ingestion on performance. The Chair of either IRB may request that a study scheduled for review by their IRB be transferred to the other IRB if the other IRB may be the more appropriate one for review. However, all VA research must be reviewed by the ETSU/VA IRB. Research involving prisoners must be reviewed by the ETSU IRB.

Except where explicitly separated in the following sections, these Policies and Procedures apply to both IRBs and all non-affiliated investigators and sites using either IRB (including those sites for which services are provided through contractual agreement). Additionally, sites where ETSU employees and students conduct research may, by agreement, use either IRB.

## **PURPOSE**

The purpose of the IRB is to ensure that humans involved in research at these institutions are afforded protection as described in the revised version of the Belmont Report, the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Guidelines, Good Clinical Practices (GCP), the Health Insurance Portability and Accountability Act of 1996 (HIPAA), all applicable Federal Regulations governing human subjects research, and the moral and ethical precepts of the Institutions.

The IRB shall have three major functions:

- ⇒ Assure the protection of human subjects involved in research or related activities;



Medical Campus East Tennessee State University /James H. Quillen  
Veterans Affairs Institutional Review Board  
(ETSU/VA IRB) Medical research IRB#00002054

## **AUTHORITY**

The policies governing the IRB are in accord with the Federal-wide Assurance (FWA) numbers indicated above and filed with the Federal Office for Human Research Protections (OHRP).

No research that involves human subjects may be undertaken at East Tennessee State University or the James H. Quillen Veterans Affairs Medical Center, or other non-affiliated site(s) using either IRB, without the prior approval of the IRB.

## **ETSU**

All individuals engaged in research that is sponsored by East Tennessee State University, conducted by or under the direction of any faculty, staff, or student or agent of ETSU in connection with his or her institutional responsibilities; conducted by or under the direction of any employee or agent of ETSU using any property or facility of ETSU; or involves the use of ETSU's non-public information to identify or contact human research participants or prospective participants must obtain ETSU or ETSU/VA IRB approval before beginning any research activities.

The IRB must review all human subject research if one or more of the following apply:

- ⇒ The research is sponsored by ETSU
- ⇒ The research is conducted by or under the direction of any employee, faculty, staff, student, or agent of ETSU in connection with his or her institutional responsibilities
- ⇒ The research is conducted by or under the direction of any employee or agent of ETSU using any of ETSU's property or facilities
- ⇒ The research involves the use of non-public information maintained by ETSU to identify or contact prospective participants or participants
- ⇒ ETSU is the recipient of a direct federal award to conduct human subject research, even where all activities involving humans are carried out by a subcontractor or collaborator
- ⇒ ETSU or ETSU/VA IRB is the IRB of record by contract or MOU

Approval by the VA Research & Development (R&D) Committee is additionally required for any research conducted at VA facilities or using VA patients, time or equipment.

Any signatory Institution may deny a research project approved by the IRB, including projects exempted by the IRB Chair. No office of any of the participating Institutions may approve a research activity that has been disapproved by the IRB.

The IRB has the authority to initiate periodic compliance reviews and/or directed audits. When necessary to assure protections of humans in research, the IRB may appoint a designee to observe the informed consent process of IRB approved research.

When issues of noncompliance or situations in which a participant in a research project has been exposed to unexpected serious harm are identified through an audit or compliance review, the IRB will promptly address such findings to assure that all research is being conducted according to Federal regulations, institutional policies and IRB policies and procedures.

The IRB has the authority and responsibility to suspend or terminate approval of research that is not being conducted in accordance with the policies and procedures of the institution or that has been associated with unexpected harm to participants or others. Any letter of suspension or termination of approval to an Investigator must include a statement of the reasons for the action by the IRB.

## **IRB Jurisdiction**

Activities must meet the definition of "research" and involve "human subjects" as defined in DHHS regulations, or be "research" and involve "human subjects" as defined in FDA regulations to be subject to the IRB's jurisdiction.

## **Definitions:**

**Research** is defined in the DHHS Federal regulations (45 CFR 46) as a “systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” Research is defined in the FDA federal regulations as any experiment that involves a test article and one or more human participants and that either is subject to requirements for prior submission to the Food and Drug Administration under Section 505(i), 507(d) or 520 (g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. Under FDA regulations the terms “research” and clinical investigation are synonymous. VA Handbook 1200.5 defines research as “the testing of concepts by the scientific method of formulating a hypothesis or research question, systematically collecting and recording relevant data and interpreting the results in terms of the hypothesis or question. 38 CFR 16.102 states that “Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”

**Human Subjects** are defined in the “Common Rule” as “living individuals about whom an investigator (whether professional or student) conducting research obtains either (1) data through intervention or interaction with the individual or (2) identifiable private information.” FDA regulations define subjects as an individual who is or becomes a participant in research, either as a recipient of the test article or control. Subjects may be either a patient or a healthy human. FDA regulations also define subjects as an individual upon whose specimen a device is used. 38 CFR 16.102 defines a human subject as meaning “a living individual about whom an investigator (whether professional or student) conducting research obtains 1) Data through intervention or interaction with the individual, or (2) Identifiable private information.

**Intervention** is defined as including both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the participant or the participant's environment that are performed for research purposes. 38 CFR 16.102(f) notes that “an intervention includes all physical procedures by which data are gathered and all physical, psychological, or environmental manipulations that are performed for research purposes.”

**Interaction** includes communication or interpersonal contact between investigator and participant.

**Test article** is defined as 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.

**Private Information** includes information about behavior that occurs in a context in

which an individual can reasonably expect that no observation or recording is taking place, and information 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).

**Investigational New Drug (IND)** means “a new drug, antibiotic drug, or biological drug that is used in a clinical investigation”

## **Determining Whether a Proposed Activity is Human Research According to DHHS or FDA Regulatory Definitions**

Activities that constitute human subject research are determined by the ETSU and ETSU/VA IRB. The IRBs delegate this decision to the IRB Chair or Vice Chair. The Chair or Vice Chair determines whether a proposal submitted to the IRB is human research according to DHHS or FDA regulatory definitions. If a protocol submitted to the IRB is determined to not be human research according to DHHS or FDA regulatory definitions, the submitter is notified in writing that the proposed activity does not fall under IRB jurisdiction. If the activity meets the FDA definition of “research” and “human subjects” as defined in FDA regulations, the IRB will adhere to all applicable FDA regulations. For drugs, the FDA regulations apply where there is any use of a drug in research except the use of a marketed drug in clinical practice. For devices, FDA regulations apply to studies where the purpose is to determine the safety or effectiveness of a device or data will be submitted to or held for inspection by FDA as part of a marketing permit.

The IRB has the sole authority to make a final determination of whether a proposed activity is human research according to DHHS or FDA regulatory definitions. Unless you are familiar enough with these regulations to be certain that the activity does not represent human research, the activity should be brought forward to the IRB for a determination. A form 129 (available at the IRB website) requesting a determination of whether the proposed activity is human research must be completed and submitted to the IRB office **prior** to beginning the project. The IRB Chair will review the form 129 and determine whether the proposed activity meets the definition of human research. The Chair or Vice Chair may not make this determination if he/she has direct involvement in the activity being examined. A written response will be returned to the submitter.

## **Oral History**

Oral History is a method of gathering and preserving historical information through recorded interviews with participants in past events and ways of life. Most oral history interviewing projects are not subject to the requirements of the regulations found at 45 CFR 46.102(d) which define research as, “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge”. While historians reach for meaning that goes beyond the specific subject of their inquiry, unlike researchers in the biomedical and behavioral sciences, they do not reach for generalizable principles or laws of nature that have predictive value and can be applied to other circumstances for the purpose of controlling outcomes.

For these reasons, oral history interviewing in general, does not meet the regulatory definition of research as articulated in 45 CFR 46. Office for Human Research Protections (OHRP) concurs

with this policy, as evidenced by the OHRP draft statement, dated 8/26/03. However, the IRB has the sole authority to make a final determination of whether a proposed activity is human research according to DHHS or FDA regulatory definitions. Unless you are familiar enough with these regulations to be certain that the activity does not represent human research, the activity should be brought forward to the IRB for a determination.

## Other activities

Case Studies	A single subject study with clear intent, before recruiting or interacting with the participant, to use data that would not ordinarily be collected in the course of daily life. The intent is to report and publish the case study.	<b>YES</b>
Case Studies	Retrospective review of a patient's medical record with the intent to report and/or publish the summary.	Retrospective review of a patient's medical record with the intent to report and/or publish the summary AND only clinically indicated interventions or data collection were performed AND data is de-identified = NO  Exception: If any aspect of the case is unusual enough that the patient might be identifiable even though normal patient identifiers are removed, then it should be submitted.)
	Retrospective review of a patient's medical records for use in an educational setting. The data will be de-identified.	<b>NO</b>

## **All Research Involving Humans Must Be Reviewed by the IRB**

The implications of engaging in activities that qualify as research subject to IRB review without obtaining such review are significant. Results from such studies may not be published or presented unless IRB approval had been obtained prior to collecting the data. To do so is in violation of East Tennessee State University Policy. It is also against University policy to use such data to satisfy thesis or dissertation requirements.

Investigators who request approval to continue research that was not previously reviewed or to use data that was collected without IRB approval face the possibility that the IRB deny the application, as the IRB cannot give post-hoc approval.

The IRB may not approve applications where the Investigator has attempted to circumvent IRB policies and procedures regarding human research by collecting data as non-research and then applying to use them as existing data. It is therefore in the Investigator's best interest to consider carefully the likelihood that he or she will want to use the data for research purposes in the future, and to err on the side of inclusion and seek IRB approval prior to commencing the work.

## **Oversight of Others Assisting in Research**

An Investigator may delegate study related activities but he or she is ultimately responsible for the conduct of the study. It is the responsibility of each Investigator to assure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise qualified to perform such under the laws of Tennessee and the policies of ETSU.

Every member of the research team is responsible for protecting participants in research. Sub-Investigators, study coordinators, nurses, research assistants, and all other research staff have a strict obligation to comply with all IRB determinations and procedures, adhere rigorously to all protocol requirements, inform Investigators of all serious and unexpected adverse reactions or unanticipated problems involving risk to participants or others, oversee the adequacy of the informed consent process, and take whatever measures are necessary to protect the safety,

rights and welfare of participants.

Regardless of involvement in research, each member of the research community is responsible for notifying the IRB promptly of any noncompliance with applicable regulatory requirements or determinations of the designated IRB of which they become aware, whether or not they are directly involved in the research.

## **Engagement**

Definitions:

Engaged: An institution becomes "engaged" in human subjects research when its employees or agents<sup>1</sup> (i) intervene or interact with living individuals for research purposes; or (ii) obtain individually identifiable private information for research purposes [\[45 CFR 46.102\(d\),\(f\)\]](#).

institution is automatically considered to be "engaged" in human subjects research whenever it receives a direct HHS award to support such research. In such cases, the awardee institution bears ultimate responsibility for protecting human subjects under the award.

Performance Site Category	Description	FWA required?	Required approval
<b>Category 1</b>	engaged in re- search with fed- eral research sup- port or direct award for study	Yes	Submit copy of site IRB approval or request that ETSU IRB be IRB of Record.
<b>Category 2</b>	engaged in re- search with no federal research support or direct award for study	No	Submit copy of site IRB approval or request that ETSU IRB be IRB of Record.
<b>Category 3</b>	Performance site not engaged in re- search with estab- lished IRB	No	Submit copy of site IRB approval or request that ETSU IRB be IRB of Record.
<b>Category 4</b>	Performance site not engaged in re- search without established IRB	No	Submit letter of permission from the appropriate institutional official stating that the research may be conducted at site.

## CHAPTER 2 - Criteria for IRB Approval

### Approvals of Research

The duties and responsibilities of the members of the IRB are best described by reproducing the statement published in 45 CFR 46.111.

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

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

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

\*When research is more than minimal risk and involves an intervention

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

## **IRB Committee Determinations**

After review, the possible actions which may be taken by the IRB are:

- ⇒ Approval of the proposal
- ⇒ Approval with stipulations
- ⇒ Defer pending receipt of additional information
- ⇒ Disapproval

A. Approved: An approval is granted if the research activity meets the criteria for approval as defined in 45 CFR 46.111 (see prior page) and no changes are recommended to the proposal.

B. Approval with stipulations: An approved pending status is given if the research meets the 45 CFR 46.111 criteria for research approval and any modifications required by the IRB require simple concurrence by the Investigator. When the modifications requiring simple concurrence are received from the investigator, the Chair or his/her designee may then review and confirm the modifications through an expedited procedure. The proposal may be referred back to the full committee if deemed necessary by the Chair or his/her designee. The research may not be initiated until a final approval letter is received.

C. Defer pending receipt of additional information: When the convened board requests substantive modifications or clarifications directly relevant to the determinations required at 45 CFR 46.111, IRB approval of the proposed research is deferred, pending subsequent review by the convened board of responsive material. The investigator will receive a written request for specific or additional information required.

D. Disapproval: Disapproval is given if the proposal does not meet the criteria for approval as defined in 45 CFR 46.111 (refer to prior page). If the IRB decides to disapprove a research activity, it will include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

## **Confidentiality**

The IRB membership must be diligent to maintain confidentiality. The Board must be free to deliberate in private without fear of coercion. With the exception of the IRB Chair or Vice-Chair, at no time may an investigator discuss deliberation content or outcomes with IRB members post-review. The IRB policy is to notify the investigator in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. The OPHRS staff will be responsible for dispatching written notifications (post-deliberation), over the signature of the Chair, to the appropriate investigator.

With the implementation of the Primary Reviewer System, designated IRB members tasked with conducting primary reviews are authorized by the convened Board to contact the Principal Investigator to discuss issues related to clarity, risk, benefits, etc.

## CHAPTER 3 - Investigator Responsibilities

### PRINCIPAL INVESTIGATOR (PI)

- ⇒ Agree to maintain current contact information, education, compliance related education / certification and applicable experience.
- ⇒ Accurately identifies research site and team members. Assures all Investigators and study personnel complete initial and continuing education in human research protections annually to remain up-to-date on Federal regulations, ETSU policies and procedures, and compliance expectations.
- ⇒ Adheres to Federal regulations, state and local laws, Institutional policies, IRB policies and procedures regarding the safety and protection of human participants and Good Clinical Practice (GCP) guidelines (if applicable to the type of research).
- ⇒ Adheres to all Federal and ETSU policies regarding the responsible conduct of research as presented at <http://www.etsu.edu/research/researchethics.htm>.
- ⇒ Ensure that the ETSU IRB and ETSU/VA IRB (registered and holding OHRP approved Federalwide Assurances (FWA) in compliance with the requirements of 45 CFR 46 , 38 CFR 17, and 21 CFR Part 56) will be responsible for the initial and continuing review and approval of the research.
- ⇒ Reports adverse events and unanticipated problems involving risk to participants and others to the IRB according to IRB policies and procedures, sponsors and appropriate Federal agencies as required.
- ⇒ Assures continuing review applications are submitted in a timely manner so that their review occurs prior to their expiration date. The Investigator acknowledges that the Federal regulations do not allow a grace period. The Investigator is responsible for being aware of the current literature in his/her field of study to assure participants are no longer placed at risk if additional risks have been identified or no benefit has been proven. The Investigator should build off previously conducted research to decrease the potential for participants to be needlessly placed at risk.
- ⇒ Acts as a liaison between the IRB and the sponsor.
- ⇒ Supervises the research process, ensuring that research is conducted in a manner which will minimize risks to subjects. Takes responsibility for assuring key study personnel are properly trained, qualified and have appropriate facilities and resources to conduct the research. Agrees to ensure that all students, faculty, associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments. Assures adherence to the study protocol. Monitors the informed consent process. Communicates regularly and effectively with their research staff. Responsible for protection of the safety and welfare of research participants.
- ⇒ Oversees external performance sites, assuring adequate staff, resources, pharmacy practices and Federal assurances with appropriate IRB approvals.
- ⇒ Assures the IRB protocol is reflected in the grant proposal for extramural or intramural support, informs the IRB of any updates or modifications to the protocol prior to their implementation and in compliance with Federal and institutional regulations.
- ⇒ Assures proper performance of the informed consent process. Retains a copy of the signed and dated informed consent document in the study file and provides a copy to the research participant.

- ⇒ Promotes compliance and maintains documents in accordance with Federal and state regulations, and sponsor and institutional policies and procedures regarding the safety and welfare of human participants. Agrees to make those records available for inspection in accordance with 21 CFR 312.68.
- ⇒ Agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, to not make any changes in the research without written IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- ⇒ Reviews and approves IRB applications, amendments and adverse events prior to their submission to the IRB, as documented by their signature on the IRB application. Submits applicable reports in a timely manner or according to published deadlines;
- ⇒ If applicable, read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.
- ⇒ Assures participant privacy (relates to person) and confidentiality (relates to data) according to HIPAA guidelines, Institutional and IRB policies and procedures.
- ⇒ Agrees to conduct the study in accordance with the relevant, current protocol and to only make changes in a protocol after obtaining IRB approval, and if funded, notifying the sponsor, except when necessary to protect the immediate safety of subjects.
- ⇒ Agrees to inform the OPHRS, VA R&D, the ETSU or ETSU/VA IRB (as appropriate) at the time of research site or records audits conducted by study sponsor, monitor or other internal, external or regulatory entity, whether announced or unannounced, for-cause or not for-cause. The initial notification (auditors on site) will be followed by a copy of the written audit findings forwarded by the auditing body to the PI, within 30-days of the PI receiving the report. The audit report must bear a stamped date indicating the receipt of the report at the local site. As available, a copy of the PI response, along with any corrective actions plans must additionally be forwarded.
- ⇒ Agrees to inform and identify to any subject, or any persons used as controls, those procedures or other interventions being used for research purposes and ensure that the requirements related to obtaining informed consent and IRB review and approval found in 45 CFR 46 are met.
- ⇒ Be responsive to IRB request for information
- ⇒ Notify IRB in writing of completed study (form 107)
- ⇒ For VA investigators, investigators are required to prepare and maintain adequate and accurate case histories. A case history is a record of all observations and other data pertinent to the investigation on each research subject. Case histories include the case report forms and supporting data including signed and dated consent forms, any medical records including, but are not limited to: progress notes of the physician, the individual's hospital chart (s), and nurses' notes. The case history for each individual must document that informed consent was obtained prior to participation in the study.

Additionally, for studies with investigational drugs or devices,

- ⇒ (for investigational drug studies) Agree to inform any subject, patients, or any persons used as controls, that the drugs are being used for investigational purposes and ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21CFR Part 56 are met. Agree to protect the rights, safety and welfare of the participants under their care.
- ⇒ Administer the drug or device only to participants under their personal supervision or the supervision of a sub-investigator
- ⇒ Supply investigational drug or devices only to persons authorized to receive it under 21 CFR 312.61; 21 CFR 812.110
- ⇒ Maintain adequate records of the disposition of the drug, including dates, quantity and use by participants. Device records must include records of receipt, use or disposition of a device including the type and quantity of a device, the receipt date, the batch number or code mark, names of all persons who received, used, or disposed of each device, records of returns, repairs or disposals.
- ⇒ Return unused supplies of the drug to the sponsor or otherwise provide for disposition of the unused drug according to regulations at 21 CFR 312.59; 21 CFR 312.62; 21 CFR 812.110
- ⇒ Maintain adequate and accurate records recording all pertinent data including the obtaining of informed consent prior to study participation. Allow authorized persons to have access to, and copy and verify records or reports (21 CFR 312.62 and 21 CFR 812.145)
- ⇒ Maintain records to meet the standards of all applicable regulations, including federal guidance, institutional standards and sponsor requirements. FDA requires record retention for drug studies to be maintained for a period of 2 years following the date a marketing application is approved for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation if discontinued and FDA is notified (21 CFR 312.62). FDA requires record retention for device studies to be maintained for 2 years after the latter of the following two dates: termination of completion or when records are no longer required (21 CFR 812.140). ETSU policy requires retention of records for five years after the study has been closed. Sponsor requirements may vary.
- ⇒ Furnish reports to the sponsor of the drug, including report shortly after completion of their participation
- ⇒ Promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug.
- ⇒ Provide sponsor with accurate disclosure statements as required at 21 CFR 312.64; 21 CFR 812.110; 21 CFR 54.4(b)
- ⇒ Assure that an IRB meeting the requirements of part 56 is responsible for initial and continuing approvals
- ⇒ For investigational drug subject to the Controlled Substances Act, take all required security precautions

- ⇒ Prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

## **Unaffiliated Investigators**

Investigators and physicians in private practice settings who are not acting as employees or agents of the institutions under the approved Federalwide Assurances noted in this policy are subject to all of the usual human protection requirements and responsibilities. Such investigators must sign an Unaffiliated Investigator Agreement (UIA), agreeing to comply with all educational requirements and to be bound by the human protection policies of the institution and its designated IRB. A copy of the fully executed document will be returned to the investigator to be added to the research records. The original copy will be maintained in the IRB Administrative records, along with the curriculum vitae for the investigator.

## **Study Coordinator and Research Staff**

- ⇒ All study personnel must complete initial and continuing education in human research protections to remain up-to-date on Federal regulations, ETSU (and VA if applicable) policies and procedures, and compliance expectations.
- ⇒ Adheres to Federal regulations, state and local laws, Institutional policies, IRB policies and procedures regarding the safety and protection of human participants and Good Clinical Practice (GCP) guidelines (if applicable to the type of research).
- ⇒ Reports adverse events and unanticipated problems involving risks to the participants and others to the IRB according to IRB policies and procedures, sponsors and appropriate Federal agencies as required.
- ⇒ Acts as a liaison between the IRB, the Investigator and the sponsor.
- ⇒ Promotes compliance and maintains documents in accordance with Federal and state regulations, and sponsor and institutional policies and procedures.
- ⇒ Assures participant privacy and confidentiality according to HIPAA guidelines, Institutional and IRB policies and procedures.

## **Department Chair, Dean or VA Service Chief (ETSU/VA applications) or Corporate Director, MSHA Dept of Research (MSHA investigators not employed by ETSU or VA )**

- ⇒ Promotes compliance with Federal and state regulations, and sponsor and institutional policies and procedures regarding the safety and welfare of human participants involved in research studies initiated from their department.
- ⇒ Reviews and approves IRB applications prior to submission, as documented by their signature on the IRB application to assure the soundness of the research design, scientific and scholarly merit in relation to the departmental capacities, and adequate staff and resources to conduct the study. (Note: ETSU's Vice Provost for Research may provide attestation that the proposal has been reviewed for scientific merit if the MSHA Corporate Director of Research is unavailable)

## **Thesis/Dissertation Chair/ Non-Thesis Faculty Advisor Responsibilities**

- ⇒ Agrees to meet with the student investigator on a regular basis to monitor study progress;
- ⇒ Agrees to be available, personally, to supervise the student investigator in solving problems, should problems arise during the course of the study
- ⇒ Advises the investigator that he/she and all study personnel must complete the ETSU human subjects training program;
- ⇒ Advises the student investigator that the project must be performed only by approved personnel according to the approved IRB application;
- ⇒ Advises the student investigator not to implement any changes to the approved IRB application before receiving IRB approval for the change(s); (see exception in Policy 10)
- ⇒ Advises the student investigator to only obtain legally effective informed consent form human participants or their legally responsible representative, (if IRB approved). Furthermore, advises the student investigator to only use the currently approved date stamped informed consent document for human participants; and that a copy of the informed consent is provided to the participant unless a Waiver or Alteration of Requirement to Obtain Informed Consent has been granted;
- ⇒ Advises the study investigator to promptly report any unanticipated problems involving risks to participants or others to the IRB in accordance with ETSU IRB Policies and Procedures;
- ⇒ Advises the student investigator that he/she must assume the responsibility for the accurate documentation, investigation, and follow-up of all possible study-related unanticipated problems involving risk to participants or others;
- ⇒ Advises the student investigator to promptly provide the IRB with any information requested relative to the project including a continuing review application;
- ⇒ Advises the student that regulations require that a change in study status, *including study completion*, be communicated to the IRB (Form 107). Additional guidance must be obtained from the IRB, if a completed Form 107 closing the study is not submitted prior to graduation.
- ⇒ Ensures that the student investigator obtains continuing review approval prior to the expiration of the study unless the study has been determined to be exempt. Further, understands that if the student investigator fails to apply for continuing review, approval for the study will automatically expire; and ensures that all study activity ceases until IRB approval is obtained.
- ⇒ Advises the student investigator that failure to comply with an IRB request of continuation review is non-compliance and that this is true even after graduation. Advises the student that failure to respond to IRB requests may constitute serious and/or continuing non-compliance which is reportable to the Office for Human Research Protection (OHRP) and other appropriate authorities, as applicable.

## Conflict of Interest

### Pertinent Definitions

**Conflict of interest** refers to instances when there is a convergence between an individual's personal financial, relational, or other interests and his/her professional obligations to East Tennessee State University (ETSU) or the James H. Quillen Veterans Affairs Medical Center (VAMC) such that an independent observer might reasonably determine that the individual's professional actions or decisions are adversely affected, distorted or otherwise compromised by the individual's personal interest. The term conflict of interest is broader and encompasses more professional activities than the term financial conflict of interest in research and for the purposes of this policy includes conflicts that may arise in review and approval of protocols submitted to the IRB when an IRB member is part of the team designing, conducting, or reporting the research presented in the protocol, or has an immediate family members involved in the design, conducting or reporting the research presented in the protocol.

**Covered individual** includes any faculty or staff member (whether fully-, partially-, or non-salaried), student, fellow, trainee, administrator or other employee who is involved in research for which the ETSU or the VAMC is responsible, or who, pursuant to the review and approval of the ETSU/VA or ETSU Institutional Review Board (IRB), conducts or engages in research involving human subjects, or is otherwise identified as involved in research by a principal investigator, chair or unit head, or other University administrative officer responsible for research activities.

**Immediate Family Members** includes spouse, domestic partner, and dependent children.

**Significant Financial Interest** includes, but is not limited to, any economic or monetary interest of the types listed in "(a)" through "(f)" below, that is held by a covered individual (or by his/her immediate family member), and that to an independent observer would reasonably appear to affect or be affected by research in which the individual is involved, or that is held by any entity in which a covered individual (or his/her immediate family member) has a financial or fiduciary interest the financial interests of which entity would reasonably appear to an independent observer to affect or be affected by the research (e.g. stock values, etc). (Such an entity may be a financially interested entity):

- A. "**Compensation interest**," meaning salary, consulting fees, wages, retainers, honoraria (including honoraria from a third party, if the original source is a financially interested company), gifts or other emoluments, "in kind" compensation from a financially interested company (or entitlement to the same), or any other thing of economic or monetary value whether for consulting, lecturing, travel, service on an advisory board, or for any other purpose not directly related to the reasonable costs of conducting the research (as specified in the research agreement), that in the aggregate have in the past 12 (twelve) months exceeded \$10,000, or are expected to exceed that amount in the next twelve months;

- B. "**Equity interest**," meaning i) any equity interest (or entitlement to the same), in a publicly-traded financially interested entity that exceeds \$10,000 in value or represents more than 5% ownership interest in any single entity (see exclusions below), or ii) equity interests, including stock options, warrants, or other convertible securities, of any amount in a non-publicly-traded financially interested entity (or entitlement to the same) whether or not financial value can be determined through reference to public prices;
- C. "**Intellectual property interest**" meaning i) royalty income or the right to receive future royalties under a patent license or copyright, where the research is directly related to the licensed technology or work; or ii) any other direct or indirect interest in a patent, trademark, copyright, trade secret, know-how or other intellectual property right where the research is directly related to the interest;
- D. "**Extraneous research payments**," meaning any non-royalty payments or entitlements to payments in connection with the research that are not directly related to the reasonable costs of the research (as specified in the research agreement between the sponsor and the institution), including any bonus or milestone payments to the investigators in excess of reasonable costs incurred, whether such payments are received from a financially interested entity or from the institution;
- E. "**Fiduciary relationship**," meaning service as an officer, director, or in any other fiduciary role for a financially interested entity, whether or not remuneration is received for such service.
- F. "**Compensation affected by the outcome of the research**" meaning compensation of any amount that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result or compensation to the investigator in the form of an equity interest in the sponsor of a covered study or in the form of compensation tied to sales of the product, such as a royalty interest.

**Exclusions.** Significant financial interest excludes, and therefore is not meant to refer to, the following types or categories of economic or monetary interest:

"**Mutual fund interests**," meaning interests of any amount in publicly traded, diversified mutual funds;

"**De minimis equity interests**," meaning stock or stock options in a publicly traded company that, when aggregated for the covered individual (and/or his or her immediate family members) meets both the following tests: it does not exceed \$10,000 in value (as measured in reference to public prices or other reasonable measure of fair market value) and does not represent more than a 5% ownership interest in any single entity;

**"Outside payments,"** meaning salary, royalties, and other payments from entities other than the University, or via the University to the individual, that when aggregated for the covered individual (and/or his or her immediate family members), over the next 12 months, are not expected to exceed \$10,000;

**"Regular research payments,"** meaning payments to the University, or via the University to the individual, that are directly related to reasonable costs incurred in the conduct of research as specified in the research agreement between the sponsor and the University;

**"University compensation,"** meaning salary, royalties, and other remuneration for services from the University;

**"Public or non-profit income,"** meaning income for service on advisory committees or review panels for public or non-profit entities, or from seminars, lectures, or teaching engagements sponsored by public or non-profit entities.

The policy of both the East Tennessee State University Campus Institutional Review Board (ETSU IRB) and the East Tennessee State University/ Veterans Affairs Institutional Review Board (ETSU/VA IRB) is to establish procedures for reporting and managing conflict of interest as it pertains to research conducted at ETSU and James H. Quillen VAMC that involves use of human research subjects. They are based on policies set forth in VHA Handbook 1200.13 and the ETSU Faculty Senate Handbook 1.17. These policies are not intended to eliminate any situation of conflict of interest, but to give an understanding of what is conflict of interest and how to report and manage it. It is the policy of the ETSU IRB and the ETSU/VA IRB that all significant financial interest, as well as other conflict of interests, be reported to the IRB for review to assure protection of the rights and welfare of participants in human subject research.

## **Investigator Conflict of Interest**

When an investigator submits a protocol, a disclosure of significant financial interest to the IRB is required for all Covered Individuals and consultants serving as study personnel involved in designing, conducting, or reporting the research presented in the protocol.

The investigator may submit this information on the IRB Potential Conflict of Interest for Investigators Form. If a potential conflict of interest is present for the investigator or any Covered Individuals or consultants serving as study personnel involved in designing, conducting, or reporting the research presented in the protocol (question number 2 is answered "yes"), then in addition, then additional forms must be submitted as follows:

- ⇒ For ETSU researchers, an ETSU Conflict of Interest Form must be completed and submitted to Vice Provost for Research
- ⇒ For VA Researchers, a VA conflict of interest form must be completed and submitted to the VA R&D Office.
- ⇒ For researchers affiliated with both institutions, both forms must be completed and submitted as noted above (two parallel pathways).

The proposal will be held by the IRB Coordinator until a management plan as detailed below is received in the IRB Office. Once the management plan is received, the IRB Coordinator forwards the proposal with the management plan to the convened board.

If the Conflict of Interest is such as to require either a VAMC or ETSU conflict management plan the approved plan must be submitted to the IRB prior to review of the protocol. The IRB Director will inform either the Vice Provost for Research or the ACOS/R of the disclosed financial interest.

If the Vice Provost for Research or the ACOS/R has already reviewed the financial interest, the Vice Provost for Research or the ACOS/R will inform the IRB in writing of all actions taken according to the relevant policies. Otherwise the Vice Provost for Research or the ACOS/R will review the financial interest and inform the IRB in writing of all actions taken according to the relevant policies. In all cases, IRB review will be held until the Vice Provost for Research or the ACOS/R has completed the review. All IRB members will be provided with a copy of the report of Vice Provost for Research or the ACOS/R.

In addition, the investigator must submit a revised Conflict of Interest Form within ten days of any change from previous disclosures, and annually disclose any changes on the continuation review Form 107.

When presenting a proposal or modification to the convened IRB, the investigator and any accompanying study staff leave the room prior to the deliberation and vote.

The investigator must comply with all recommendations of the IRB Office to minimize conflict of interest.

## **Managing Conflicts of Interest**

In addition to actions taken by the Vice Provost for Research or the ACOS/R, the IRB reviews the management (resolution) plan. The IRB may accept the plan, request modifications, or disapprove the research. The IRB makes the final determination and may take the following actions to manage, reduce, or eliminate conflict of interest.

- ⇒ Public disclosure of significant financial interests
- ⇒ Monitoring research through oversight/audit
- ⇒ Modify research plans and/or ICD
- ⇒ Disqualification from participating in research
- ⇒ Divestiture of significant conflict of interest or
- ⇒ Severance of relationship that create actual or potential conflicts
- ⇒ More frequent continuing review
- ⇒ Disapproval of research

If a conflict of interest is identified after a study has been approved or initiated, the Chair or VPR will consult with the IRB and, if appropriate, the R&D Committee to identify the impact of the conflict on the protocol and the research subjects to ensure actions are taken to decrease the impact. Corrective actions may include:

- ⇒ Modifying the protocol and ICD
- ⇒ Re-consenting subjects
- ⇒ Removing the investigator from the subject selection process
- ⇒ Supervision of the protocol by independent reviewers and/or
- ⇒ Requiring disclosure in all publications/presentations resulting from the research

The conflict must be managed so that it does not affect the rights and welfare of participants. Disclosure alone can not be used to manage a conflict of interest that might affect participant rights and welfare.

An inability to resolve these issues will be reported to the ETSU President, and if applicable, the VA Medical Center Director, through the appropriate committees.

## **Failure to Comply with Conflict of Interest Policy**

If an investigator fails to comply with this policy or with the corrective actions relating to it, the Chair will report this to the VPR, and if applicable, the Medical Center Director. Failure to comply may also result in additional conditions or restrictions including:

- A. Termination of the protocol
- B. Removal of the investigator from the research team
- C. Revocation of the privilege to conduct research at ETSU or within the VA
- D. Sanctioning by PHS, FDA (or other applicable entities)

## **Human Research Protections Training**

The IRB has contracted with a group of collaborating professionals through the University of Miami to manage and provide the necessary educational materials for Investigators engaged in research involving humans. The **Collaborative Investigator Training Initiative (CITI)** is a required course for those Investigators and study personnel who have **not previously** completed ETSU initial or continuing human research training requirements. Human research protections training must be completed prior to submitting an application for IRB review. IRB applications will not be accepted from Investigators who have not successfully completed the training. **In addition, all study personnel listed on the application will have to complete CITI.**

**Study Personnel**- anyone who is responsible for the design or conduct of the study. This list may include, but not limited to, sub-investigator (Co-investigators), research assistants, research coordinators, research nurses, etc.

Modules from each pathway will take approximately 10 to 30 minutes. The course does not have to be completed in one sitting and the modules can be completed in any order. A combined score of 80% or better is required for passing. To complete the CITI training, Investigators and all key study personnel should follow the instruction below:

### **First Time Users of CITI Training Program**

1. Go to [www.citiprogram.org](http://www.citiprogram.org) and click on "Register for the CITI Program", then submit
2. Under ALL OTHERS, Choose "East Tennessee State University" and submit
3. Select your Username and Password, then submit. This is what you are going to use to go in and out of the program
4. Fill out Registration Page, then submit information
5. Select your group below and submit :
  - Group 1- Biomedical not affiliated with VA
  - Group 2- Biomedical affiliated with VA
  - Group 3- Social and Behavioral not affiliated with VA
  - Group 4- Social and Behavioral affiliated with VA
6. On the Learners Menu, click on "Basic Course (required; Status Incomplete)"
7. Complete the Required modules (top of page).
8. To get access to the optional modules (not part of required training unless requested), click on "View the Grade Book" after completing the test on the last module. Scroll down. This will give you all the score of the modules you have completed and give you access to the optional modules.
9. It is important that you print the certificate by clicking on "Print a certificate of completion" after finishing the test on the last module. This will trigger an email to the IRB, letting us know you completed the training.

If you have already registered at CITI, just enter your username and password. This will take you to where you left off.

The IRB might require that you complete additional requirements from the "Optional Modules" section. However, you do not have to complete these modules until notified to do so.

## **Ongoing Training Requirement**

The IRB requires that all Investigators and study personnel have ongoing training in the area of human research protections. As studies are submitted for continuing review to the IRB, the staff will check to see that this requirement is met.

The IRB Office will provide a reminder when recertification is required. Failure to meet this requirement will delay the continuing review process, which may result in expiration of study approval.

Additionally, faculty members are invited to contact the IRB Office to schedule a topic specific seminar, if further training is necessary. In-depth instruction on specific topics is also available, and will be scheduled by IRB staff in response to departmental request.

In addition, basic training materials, including the *Belmont Report*, and links to the pertinent Federal regulations and other resources, are available on the IRB website <http://www.etsu.edu/irb>. All IRB forms and related information are also posted on the website.

In addition, the Policies and Procedures Manual is also available on-line, as is specific guidance directed to graduate students, residents, etc.

The IRB Staff create a monthly newsletter containing information about new developments in policies, procedures and regulations as well as a spotlight on a monthly topic. This newsletter is forwarded electronically to the Director, Office of Information Technology, for campus-wide distribution, and to the VA Administrative Officer for VA distribution.

## CHAPTER 4– IRB Review: Exempt, Expedited, and Full

### Levels of IRB Review

All research involving humans that falls under the jurisdiction of the IRB for review and approval must meet the criteria for one of the following methods for review:

- ⇒ Exempt from IRB Committee Review
- ⇒ Expedited Review
- ⇒ Full Review



**No human participants may be enrolled or recruited prior to receipt of written final approval of the application from the IRB for exempt, expedited and/or full reviews.**

### Exempt Review

Exemption does not mean “Do nothing”.

In each instance, the investigator will make the initial request for exempt status and the IRB Chair will make the final determination. If the research is submitted by the IRB Chair, either the Vice Chair or the Vice Provost for Research at East Tennessee State University will make this determination.

Neither the Chair nor the Vice Chair may review for approval research studies submitted for exempt or expedited review from their respective departments or divisions (for larger departments). In the absence of the Chair and Vice Chair, the Vice Provost for Research or the Associate Chief of Staff for Research will review the determination. If upon this review the determination of exemption is not upheld, the investigator will be informed and provided with the reasons for denial of exemption. The protocol may then be submitted for either expedited or full review, as appropriate to the level of risk, to the IRB.

The institution retains the option under the assurance to not claim the options provided for exempt status, but instead choose to require IRB review.

Documentation for all exemptions will include citation of the specific category justifying the exemption.

Research that is determined to be exempt from IRB review is not exempt from protection of human subjects. All exempt research is subject to human subject protections and ethical standards.

## **Categories for Exempt Approval:**

Only studies that meet one or more of the six categories of exempt activities as delineated by DHHS Regulations (45 CFR 46 (101)(b)) are eligible to be given exempt status. NOTE: These categories do not apply to prisoners and categories 1-5 do not apply to FDA regulated research. For a list of the categories that qualify for exempt approval, check the IRB website at [www.etsu.edu/irb](http://www.etsu.edu/irb).

## **Ethical Standards:**

Studies submitted requesting exempt status will be reviewed by the Chair or Vice Chair to determine whether the research fulfills the organization's ethical standards. The standards are as follows:

1. The research holds out no more than minimal risk to the participants.
2. The selection of participants is equitable.
3. If the study includes recording of identifiable information, there are adequate provisions to maintain the confidentiality of the data.
4. If the study includes interactions with participants, there is a consent process that discloses such information as:
  - a. that the activity involves research
  - b. a description of the procedures
  - c. that participation is voluntary
  - d. the name and contact information for the investigator
5. The research has adequate provisions to maintain the privacy interests of participants.

If the Chair or Vice Chair identifies ethical concerns in the research submitted for exemption, the study will not be exempted.

## **Confidentiality**

Review of Existing Charts and Records of Patients: Effective, April 14, 2003, *The Health Insurance Portability & Accountability Act of 1996* (HIPAA) apply. Pursuant to the privacy provisions of HIPAA, researchers must take precautions to protect the privacy of individually identifiable health information, or "protected health information," (PHI). Under the HIPAA Privacy Rule, some research that was exempt from the rule (45 CFR 46) and/or IRB review now requires an authorization, signed by the subject, for release of PHI or a Waiver of Authorization. NOTE: The HIPAA Privacy Rule does not apply to research that is not supported by nor requires access to health information.

Charts and patient records that are maintained as a standard part of clinical care may be used in research and may be exempted from IRB review under 45 CFR 46.101(4) or qualify for waiver from informed consent (§46.116(d)(1)-(4)) or waiver from signed consent (§46.117(c)(1) or (2)), if these sources are publicly available or if the information contained on the charts or in the records is recorded or compiled by the investigator in such a way that the patient cannot be identified directly or through identifiers linked to the patient. (There are 18 designated identifiers under HIPAA). If an investigator wishes to use patient charts or records, he or she shall submit the protocol to the IRB Chair for final determination of exempt status or appropriateness of waiver. The final approval for granting a waiver must be made by the IRB. The method for ensuring the protection of data and the confidentiality of the patient must be explicitly described in the protocol.

## **Procedures for Requesting an Exemption**

The following documents are required for an exempt review:

- ⇒ A complete IRB application (Form 103) with original signature. (form 103 available on the IRB website). (If the PI is a student, the chair or committee chair must be named as a co-investigator on the application).
- ⇒ Narrative using the template on the IRB website
- ⇒ Copy of the final ad intended for participant view or use, if any
- ⇒ Copy of all research related measures (questionnaires, surveys, etc)
- ⇒ Conflict of Interest form
- ⇒ Unaffiliated Investigator Form, if applicable
- ⇒ Students must submit a completed Faculty Assurance Statement
- ⇒ CV of PI
- ⇒ If study has an associated contract, a copy of the contract, or at minimum, a copy of any contract pages referencing provisions for medical care or other care and services for research-related injury

Please submit the original of all materials.

The IRB Coordinator will receive the proposed project and review for completeness, including attachments of any pertinent documents.

- ⇒ If any necessary documents are not present or proposed documents are incomplete, the IRB Coordinator will contact the study staff and request missing items or completion of the documents.
- ⇒ If documents are complete, then the IRB Chair will evaluate each proposed study and determine whether the proposed study meets exempt status.
- ⇒ The decision will be communicated in writing to the PI.

## **Modifications**

Any proposed changes to an exempt study must be submitted to the IRB for review and approval prior to implementation. Some modifications to the research may change the review status and require the investigator to submit an application for expedited or full review. (refer to modification policy)

## **Expedited Review**

Expedited review does not mean “fast”, but rather that certain research meeting the specified criteria may be reviewed by the IRB Chairperson, the Vice Chair; or two or more IRB members who have been selected based on their expertise and experience, not at a convened Committee meeting.

## **Categories for Expedited Approval**

Only those research activities that present no more than minimal risk to human subjects AND involve only categories delineated may be reviewed by the IRB through the expedited review procedure authorized by [45 CFR 46.110](#) and 21 CFR 56.110. For a list of the categories that qualify for expedited approval, go to the IRB website.

Expedited review **MAY NOT** be used if:

- X** research is minimal risk but does not appear in one of the listed categories
- X** research involves greater than minimal risk.
- X** research where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- X** research is classified and involves human subjects.



**Investigators should remember that even though research may be eligible for expedited review it still remains subject to the requirements of informed consent unless waived.**

## **Procedures Required for Expedited Review**

Because a study meeting these criteria is reviewed by the appropriate IRB Committee Chairperson, the Vice Chair, or two or more IRB members who have been selected based on their expertise and experience, there are no deadlines for submission. However, in reviewing the research, the Chairperson or designated IRB Member(s) may exercise all of the authorities of the full Committee except he or she may not disapprove the research. The Chairperson or designated Committee Member(s) may refer the application to the Committee for review or request that the study be reviewed by another IRB Committee member with an appropriate area of expertise.

The following documents are required for expedited review:

- ⇒ A complete IRB application (Form 103) with original signature ( form 103 available on the IRB website). (If the PI is a student, the chair or committee chair must be named as a co-investigator on the application).
- ⇒ Narrative using the template on the IRB website
- ⇒ All proposed Informed Consent Documents using the template available on the IRB website with version date as footer or header, if applicable
- ⇒ Complete protocol, when applicable
- ⇒ Copies of the final ad(s) intended for participant view or use.
- ⇒ Copy of all research related measures (questionnaires, surveys, tests, interview question outline, including email solicitations, etc)
- ⇒ Conflict of Interest form
- ⇒ Unaffiliated Investigator Form, if applicable
- ⇒ HIPPA Authorization to Use and Disclose Information Form, if applicable
- ⇒ A copy of the grant application, if applicable
- ⇒ For student studies, a completed Faculty Assurance Statement
- ⇒ CV of PI
- ⇒ Any required supplemental submission forms
- ⇒ **If study has an associated contract, a copy of the contract, or at minimum, a copy of any contract pages referencing provisions for medical care or other care and services for research-related injury**



Please submit the **original** and three (3) copies of all materials.

The IRB Coordinator will receive the proposed project and review for completeness, including attachments of any pertinent documents.

- ⇒ If any necessary documents are not present or proposed documents are incomplete, the IRB Coordinator will contact the study staff and request missing items or completeness of the documents.
- ⇒ If documents are complete, then the IRB Chair will evaluate each proposed study and determine whether the proposed study meets expedited status. The Chair and/or Coordinator will forward a copy of the proposed documents to expedited reviewers for review.

- ⇒ If a proposed study is not approved under the expedited criteria, the PI has the responsibility to submit the study for full review, as appropriate to the level of risk, by the IRB.

## **Results of Expedited Review**

Following the review by the IRB Chairperson or designated expedited reviewer(s), the investigator will receive a letter addressing one of the following possible determinations:

- ⇒ The study is **approved**, in which case a copy of the consent documents with the stamped approval period will be sent with the final approval letter and the study may begin.
- ⇒ The study is **approved with specified, non-substantive revisions**. The Investigator will receive a letter clearly indicating the required modifications. Upon receipt of the changed documents, the Committee Chairperson will verify that the appropriate additions/corrections were made and will approve the study. A final approval letter will be sent to the Investigator including the consent documents stamped with the corresponding approval period. If requested changes are substantive, the reviewers may choose to defer the study to the board.
- ⇒ **Study Deferred to Full Board**—The IRB Chairperson or designed expedited reviewers may refer the study to the Committee. If the application is referred for Committee review, the Investigator will be notified by the IRB. Whenever possible, the proposal will be included on the agenda for the next regularly scheduled Committee meeting. The reviewers may also request additional information, to be included for Committee review and, when appropriate, may request that the Investigator be present at the meeting.

## Full Committee Review



A submitted study meeting this criteria is reviewed by IRB members, including primary reviewers with an appropriate area of expertise prior to the convened meeting. Copies are sent to the IRB members in their packets; therefore, a submission deadline is strictly enforced. Check the IRB website for meeting and deadline dates.

The following documents are necessary for full review:

For initial full review protocols, The Principal Investigator (PI) is responsible for submitting one original plus 30 copies of the following typed documents:

- ⇒ Form 103, and any attached documents such as MSHA Research Request Form (If the PI is a student, the chair or committee chair must be named as a co-investigator on the application).
- ⇒ Narrative completed per guidelines
- ⇒ proposed informed consent document
- ⇒ any recruitment materials, including any advertisements intended to be seen or heard by potential participants
- ⇒ any questionnaires, surveys, testing forms and/or introduction letters associated with the study and intended for participant use or view
- ⇒ Investigator CV
- ⇒ Conflict of Interest Form
- ⇒ For student studies, a completed Faculty Assurance Statement
- ⇒ any Supplemental Submission Forms for Vulnerable Populations

In addition, the PI submits one copy of the following:

- ⇒ full protocol
- ⇒ any relevant grant application (Investigators who are seeking funding, whether federal or otherwise, must submit a copy of the funding packet for review)
- ⇒ investigator's brochure, if there is one (investigational drugs only per 21 CFR 312)
- ⇒ for HHS supported multicenter clinical trials, a copy of the HHS approved sample informed consent document\*
- ⇒ for HHS supported multicenter clinical trials, a copy of the complete HHS approved protocol
- ⇒ If study has an associated contract, a copy of the contract, or at minimum, a copy of any contract pages referencing provisions for medical care or other care and services for research-related injury

**It is strongly recommended that investigators submit one copy of the packet to the IRB Office on the Thursday before the posted submission deadline for administrative review. This will help ensure that your submission to the IRB is complete before you make the 30 copies.**

## Primary Reviewers

To improve the quality and efficiency of IRB review, the Primary Reviewer system will be used to conduct initial review of proposals presenting more than minimal risk. Under this system, a

minimum of two members will be assigned to each protocol to be reviewed at the full-committee meeting. Each initial full review is assigned a Primary Scientific Reviewer and a Primary Informed Consent Reviewer. The assigned Primary Scientific Reviewer will have scientific or scholarly expertise in the area of the research adequate to the complexity and scope of the research. A Primary Informed Consent Reviewer will also be assigned for each initial full review.

Primary Reviewers are IRB members who are appointed each month to the task by the IRB Chair. Selection is based on consideration of the protocol and reviewer's area of expertise, dedication to continuing education and availability to accept new and continuing research.

The reviewers should conduct an in-depth review of all pertinent documentation. Reviewers may contact the investigator for clarification or additional information.

## **Convened Meetings**

Applications for consideration at the convened meeting of the IRB are distributed to the Primary Reviewers and the members of the IRB prior to the convened meeting. Initial reviews of research must be conducted by the IRB at convened meetings at which a majority of the members are present, including at least one member whose primary concerns are in the non-scientific areas, except where expedited review is appropriate under HHS Regulations at 45 CFR 46.110(b)(1) for the categories of research listed in the Federal Register of November 9, 1998. Approval of research is by a majority vote of this quorum. Members with a vested interest in any protocol may not participate in the deliberation and voting process, although these members may participate in the discussion of such proposals. Initial full reviews will be individually presented, and discussed by the IRB as a whole group. In conducting the initial review of proposed research, the IRB reviews information in sufficient detail to make the determinations required under DHHS Regulations at 45CFR46.111. Approval will only be granted after substantive review and careful consideration of the determinations required under HHS Regulations at 45 CFR46.111.

## **Presentation by PI**

The Principal Investigator will be asked to attend the meeting in which his/her proposal will be discussed. If the investigator cannot attend the meeting, a qualified, knowledgeable representative (e.g., M.D. or Ph.D. for medical protocols) may be sent. In the event of a study being presented by a thesis or dissertation student, the student's (knowledgeable) advisor or faculty co-investigator should attend the meeting to support the presentation of the protocol alongside his/her student as well. (When a student is indicated as the Principal Investigator on the Form 103, a faculty member must be identified as a Co-investigator). The IRB members are encouraged to ask the investigator for a synopsis of the research and to explain or clarify points that bear adversely on the risk/benefit ratio or to supply missing materials.

The full IRB Committee is informed of the Primary Reviewer's findings during the convened meeting. At the meeting, following the investigator's presentation, the Primary Reviewers will initiate discussion by presenting an overview of the goals, design, study procedures and safety

procedures for each study. Particular attention will be paid to the Risk/Benefit Ratio of the investigations and the adequacy of the Consent Forms in conveying the procedures, implications and full intent of each study. Problems identified by the Primary Reviewers or by other IRB members will be discussed and suggestions for any necessary changes will be agreed upon by the IRB.

## **Results of Full Committee Review**

After review, the possible actions which may be taken by the IRB are:

After review, the possible actions which may be taken by the IRB are:

- ⇒ Approval of the proposal
- ⇒ Approval with stipulations
- ⇒ Defer pending receipt of additional information
- ⇒ Disapproval

## **Approvals:**

If the proposal is approved or approved with stipulations, members also decide on the interval for the ongoing review of the study based on the degree of risk to human subjects. Continuing reviews for approval beyond the initial year will be annual reviews or other predefined review periods not to exceed one (1) year. (refer to continuing review policy)

If the proposal is approved with stipulations that require simple concurrence by the investigator, the OPHRS staff informs the investigators of the stipulations and the actions required by the investigator to satisfy them. If the convened board stipulates certain provisions requiring simple concurrence by the investigator, the IRB Chair or another IRB member designated by the Chair may subsequently approve the revised protocol on behalf of the IRB under an expedited review procedure. If necessary, response to stipulations may be submitted to the full IRB for reconsideration.

Upon subsequent approval of protocols by the full IRB, Chair, or Secondary Reviewer, a letter over the signature of the Chair subsequently informs the investigator of the determination/action of the IRB, including the determined period of continuing review. The IRB coordinator will release approvals for the protocol only after the required changes have been made, received by the IRB Office, and approved as indicated above.

The approval letter(s) instruct the PI that any changes in approved projects must be reviewed and approved before they are initiated; that any unanticipated problems involving risks to participants or others must be reported to the IRB; and that monitoring will occur. The frequency of monitoring will be determined by the IRB at the time of initial or continuing review (as noted above and in continuing review policy), and investigators will be informed of this period.

An approved copy of the Informed Consent document will also be returned to the investigator. Each page of the Consent will bear an IRB stamp of approval and expiration date over the initials of either the IRB Chair, Vice Chair, Director or IRB Coordinator. The approved ICD must have a version date and an area for the subject to initial each page of the ICD in the footer area.

Particularly for ICDs used in medical research, the IRB may recommend that the *time* of participant signature be added to signature area of the consent document. An original, stamped, dated and initialed copy of the approved Informed Consent, mirroring the last approved ICD forwarded to the investigator, will be maintained in the OPHRS located on the campus of East Tennessee State University.

Additionally, copies of all correspondence, including a copy of approved ICD, are forwarded to the VA Research & Development (VA R&D) office for all VA investigators.

### **Deferral Pending Receipt of Additional Information**

When the convened board requests substantive modifications or clarifications regarding the protocol or informed consent that are directly relevant to the determinations required by the IRB approval of research under HHS Regulations at 45 CFR 46.111, IRB approval of the proposed research is deferred, pending subsequent review by the convened board of responsive material. The investigator will receive a written request for specific or additional information required.

Approval of the project will not be granted until all deficiencies are corrected to the satisfaction of the IRB. The IRB may request that an outside consultant review the application.

### **Disapproval**

In the event that a proposal is disapproved at the meeting, the investigator will be notified in writing of the Board's disposition along with an invitation to respond either in person or in writing. The appeal process will additionally be made available. The investigator may alternately choose to represent the protocol rather than appeal. (See Appeal policy)

### **Research at the VA**

The James H. Quillen Veterans Affairs Medical Center is governed by VHA, DHHS, ORO and FDA regulations protecting the rights, safety, and confidentiality of human subjects in research. The VA Research & Development Committee (VA R&D) functions under the mandate of codes and articles such as, Title 38 in the Code of Federal Regulation and VHA Handbook 1200.5. Ethical precepts included in The Belmont Report, the Nuremberg Code, the Declaration of Helsinki and Good Clinical Practice also apply. An approved Federalwide Assurance for the ETSU/VA IRB is on file with the Department of Health and Human Services Office for Human Research Protection.

Completion of compliance course(s) in the ethical conduct of human subject research is required **prior to submission**. Compliance education is verified at the time of submission. Research proposals/protocols will not be accepted by the VA R&D Administration until credentialing has been verified and the Principal Investigator and members of the research team (e.g., co-sub-investigator, research coordinators, etc.) have completed the VA CITI course, or a similar course (s). Proof of course completion will be required.

**NOTE:** Investigators seeking to conduct research at the James H. Quillen Veterans Affairs Medical Center (VAMC) \*must additionally seek approval from the VA R&D prior to initiating research activity. VA R&D approval is, however, contingent upon IRB approval. Should assistance be required, contact the VA R&D Administration. (Contact Information on last page)

\*Using Veteran population, VA Facility, equipment or VA time, VA employees.

Go to [www.etsu.edu/irb](http://www.etsu.edu/irb) for VA submission Guidelines.

## CHAPTER 5 - Informed Consent

Informed Consent is the knowing consent of an individual or his/her legally authorized representative which is obtained without undue inducement or element of force, fraud, deceit, duress, or other forms of constraint or coercion. Informed consent is not just a form or signature, but a process of information exchange that includes:

- ⇒ subject recruitment materials
- ⇒ verbal instructions
- ⇒ written materials
- ⇒ questions/answer session
- ⇒ agreement documented by signature

The investigator must obtain legally effective written informed consent prior to enrolling a subject in a research project unless approval has been granted by the IRB to waive the requirement for informed consent or waive the requirement to obtain written documentation of informed consent. The IRB reviews all informed consent documents for adherence to Federal regulations regarding the required elements of informed consent and for assurance of the adequacy of the information contained in the informed consent. The IRB has the authority to observe or to have a third party observe the consent process and the research (refer to the quality improvement policy). The consent process should provide ample opportunity for the investigator and the participant to exchange information and ask questions. The possibility of coercion or undue influence must be minimized. The IRB evaluates such factors as who will obtain the informed consent, and the timing, including any waiting period, for obtaining consent. In addition, the IRB evaluates how and what information will be communicated during the consent process.

The ETSU IRB and ETSU/VA IRB require the use of a form (see IRB web site for template). Policies do not allow informed consent to be obtained using a short form written consent document. Every page of the approved informed consent must be date-stamped and initialed by the IRB Chair or Coordinator and initialed by the participant. The IRB will affix the approval and expiration dates to all approved informed consent documents and stipulate in approval letters that copies of the approved document(s) must be used in obtaining consent.

Whenever the IRB requires documentation of informed consent, before a subject can participate in the research, the consent document must be signed and personally dated by the subject or by the subject's legally authorized representative, and by the person who conducted the informed consent discussion. During the period of prospective enrollment, the investigator (or qualified designee) must ascertain, either during the preliminary telephone interview (interest query) (note: telephone inquiry prohibited by VA policy- see Policy 16), face-to-face encounter or by review of the medical history, the subject's ability to provide consent (HIPAA regulations regarding sharing/access to PHI apply). Before participation in the research, the subject or the subject's legally authorized representative must be given a copy of the signed and dated written informed consent

form and any other written information provided to the subjects. During a subject's participation in the research, the subject or the subject's legally authorized representative must be given a copy of the signed and dated consent form updates and a copy of any authorizations to PHI, or amendments to the written information originally provided.

Unless the IRB has waived the requirement for informed consent (§46.116 (c) 1-2 or (d)(1)-(4)), or waived the requirement to obtain written documentation of informed consent as provided in §46.117(c)(1) or (2), informed consent must be documented in writing with a long form. The consent document must contain the elements of informed consent required by the regulations. The investigator is required to give the participant or the participant's legally authorized representative adequate opportunity to read the consent document before it is signed. The form may be read to the participant or the participant's legally authorized representative. The signature of the participant or the participant's legally authorized representative must be obtained on the informed consent document bearing the most recent IRB approval stamp. Additionally, the participant or the participant's representative must date the informed consent document. A copy of the informed consent document must be given to the person signing the form. These actions must be noted in the study records (e.g., participant given a copy of the signed ICD on [date] by [name]). In certain types of research, it may also be useful to also include the time of signing (ICD) along with the signatures and date.

## **Level**

The informed consent document must be written using language that can be understood by someone reading at the seventh grade level. Medical terminology should be avoided or defined. The consent form is a statement addressed to the participant and should read as such. Separate forms may be required for different participant groups (parents, children) as well as for release of particular types of information (photographs, audiotapes videotapes).

## **Version Date**

All Informed Consent Forms must bear a version date in the footer on each page of the consent. The version date must be updated whenever a revision is made to the informed consent document. (refer to modification policy)

Always use the most current approved IRB stamped ICD when obtaining consent.

## **Elements**

The informed consent document must contain all the required elements of Informed Consent, as well as any pertinent additional elements.

## **Required Elements of Informed Consent**

In seeking informed consent the following information shall be provided to each subject (§46.116, 21CFR50, 21CFR56):

- ⇒ A statement (introduction) that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental
- ⇒ Possible Risks/Discomforts - state any known risks, side effects. In double-blinded studies, risks or possible reactions should be listed separately for each agent in each arm of the study.
- ⇒ Possible Benefits - describe potential benefits which might be expected by the subject and society in general. If the individual will receive no benefit this must be stated.
- ⇒ Financial Costs - list possible financial costs to participant
- ⇒ A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. If there are no alternatives, so state. (If there are alternatives, please describe them.)
- ⇒ Confidentiality - A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. (include statement that notes the possibility that specific regulatory authorities may inspect the records (i.e., FDA, DHHS))
- ⇒ Voluntary Participation - note that participation is voluntary and subject may refuse to participate with no penalties. List point of contact by name and phone number to call to terminate participation (two names and two different telephone numbers are required).
- ⇒ 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.
- ⇒ Injury / Complications - 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. Describe in detail how complications will be handled.
- ⇒ 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.

## Additional Elements of Informed Consent

Additionally, one or more of the following elements of information must also be provided to each subject if required as indicated below:

- ⇒ The consent process must include a statement that the particular treatment or procedure may involve risks to the participant which are currently unforeseeable **UNLESS** the risk profile of all research-related interventions is well known **and** the research involves no investigational drugs or devices.
- ⇒ The consent process must disclose that the particular treatment or procedure may involve risks to the embryo or fetus, if the participant is or may become pregnant, which are currently unforeseeable **UNLESS** the research excludes women of child bearing potential and pregnant women **or** the risk profile of all research interventions or interactions on embryos and fetuses is foreseeable **or** there is no reasonable expectation that this research causes risks to fetuses or embryos.
- ⇒ The consent process must disclose anticipated circumstances under which the participant's participation may be terminated by the investigator without regard to the participant's consent **UNLESS** there are no anticipated circumstances under which the participant's participation will be terminated by the investigator without regard to the participant's consent.
- ⇒ The consent process must disclose any additional costs to the participant that may result from participation in the research **UNLESS** there are no costs to the participant that may result from participation in the research.
- ⇒ The consent process must disclose the consequences of a participant's decision to withdraw from the research **and** procedures for orderly termination of participation by the subject **UNLESS** there are no adverse consequences (physical, social, economic, legal, or psychological) of a participant's decision to withdraw from the research.
- ⇒ The consent process must disclose that significant new findings developed during the course of the research which may relate to the participant's willingness to continue participation will be provided to the participant **UNLESS** significant new findings during the course of the research which may relate to the participant's willingness to continue participation are unlikely.
- ⇒ The consent process must disclose the approximate number of participants involved in the study **UNLESS** the approximate number of participants involved in the study is not important to a decision to take part in the research.

If measures to prevent pregnancy should be taken while in the study, this should be explained in the consent process. If relevant animal data are available, the significance should be explained to potential participants. All Public Health Service (PHS) studies require that when HIV testing is conducted or supported by PHS, individuals whose test results are associated with personal identifiers must be informed of their own test results and provided the opportunity to receive appropriate counseling unless exception criteria are met. This procedure must be described in the ICD.

When in the IRB's judgment, additional information would be meaningful to participants, the IRB will require that the additional information be given to participants.

## **VA Required Paragraphs**

The only informed consent document that the VA can recognize is the VA Form 10-1086. A VA Form 10-1086 must be used as the consent form for all VA research. The VA Form 10-1086 must incorporate all the elements required by regulations.

Refer to the IRB website, [www.etsu.edu/irb](http://www.etsu.edu/irb), for the most current required language for VA consents.

VA 10-1086s must contain Signature and date lines for the following:

- ⇒ subject or the subject's legally-authorized representative,
- ⇒ witness whose role is to witness the subject's or the subject's legally-authorized representative's signature, and
- ⇒ person obtaining the informed consent

VA consents must include information about where and how a veteran could verify the validity of a study and authorized contacts.

For VA studies, in the event that someone other than the investigator will be conducting the consent interview or obtaining consent, the investigator must provide a formal delegation of the responsibility of obtaining informed consent. The delegate must have received appropriate training (completed CITI IRB requirements as well as protocol-specific training by the PI)

The informed consent form must be signed and dated by the subject or the subject's legally authorized representative, a witness whose role is to witness the subject's or the subject's legally authorized representative's signature and the person obtaining the informed consent.

The original signed 10-1086 is maintained by the Principal Investigator in the study file, a copy is given to the subject, a copy of both the ICD and the (HIPAA) Authorization scanned into the electronic medical record of the subject, and an annotation is made in the progress notes indicating that the ICD had been scanned into the electronic record.

## **Payments**

Payments to participants for their participation in a research study must be IRB approved. The amount must be commensurate with the expected contributions of the subject. The amount and terms of the payment (check or cash, etc, as well as timing of receipt of compensation) must be stated precisely. The Informed Consent form should reflect a fair and appropriate amount that does not place undue pressure (coercion) to the volunteer.

## **For Non-English Speaking Participants**

Regulations require that informed consent be obtained in a language that is understandable to the participant (or to the participant's legally authorized representative). Validated translations of consent forms must be available for non-English speaking subjects. To address possible questions or concerns raised by the prospective subject, a qualified translator must be present

and may act as a witness. Documentation of the qualifications of the translator must be added to the research records and available for administrative or QI auditing upon request.

Unless a waiver is granted by the IRB, a long consent written in a language understandable to the participant and embodying all the required elements is required by the IRB to document the consent process. The IRB requires that the appropriately translated ICD be submitted to the IRB for review and approval prior to their use in enrolling subjects.

The IRB may use expedited review procedures in approving such documents if the English language ICD has already been approved, and the investigator attests in writing to the accuracy of the translation.

## **Legally authorized representative**

A legally authorized representative shall be 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. Legally authorized representative is synonymous with legally acceptable representative. [21 CFR §50.3(l)] [45 CFR §46.102(c)]

A signature line for legally authorized representatives may only be included on the consent document if the IRB approves the enrollment of participants based on the permission of a legally authorized representative.

For cognitively impaired veterans subjects who would be enrolled in research studies at a Department of Veteran Affairs Facility, permission is obtained from a health care agent appointed by the person in a Durable Power of Attorney for Health Care (DPAHC) or similar document, court-appointed guardians of the person, or from next-of-kin in the following order: Spouse, Adult child (18 years or older), parent, adult sibling (18 years or older), grandparent, or adult grandchild (18 years or older).

For non-VA studies, in the case of an incompetent individual or an individual who lacks decision-making capacity, the individuals' health care decision maker (LAR) is designated in order of preference as one of the following:

- A. Court-appointed Conservator or Guardian of the individual with authority to make health care decisions for the patient
- B. Person named in the patient's Durable Power of Attorney for Health Care ( DPAHC)
- C. If the patient does not have a court-appointed guardian or conservator, AND does not have a person authorized to act under a Durable Power of Attorney for Health Care, then both of the following must be true for the individual identified to serve as the surrogate decision-maker for this patient:

1. The person identified above is:

- ⇒ An adult
- ⇒ Who has exhibited special care and concern for the patient
- ⇒ Who is familiar with the patient's personal values AND
- ⇒ Who is reasonably available to serve as a surrogate

2. It appears as though the person can make health care decisions for the patient in accordance with the patient's individual health care instructions, if any, and other wishes, if known to the health care decision maker. If the patient has not given individual health care instructions, and the patient's specific wishes are not known, the health care decision maker can make a determination of the patient's desires or best interests in light of the patient's personal values and beliefs to the extent they are known.

This person may include, in order of descending preference, the patient's spouse, the patient's adult child, the patient's parent, the patient's adult sibling, any other adult relative of the patient or another adult who satisfies the requirements listed above.

The investigator must indicate in the application that he/she is requesting to utilize consent of a health care decision maker. The IRB must approve the use of an LAR. The IRB will review the rationale for this request, and ensure there are appropriate safeguards in place.

In addition, if research involving adults who are unable to consent is being conducted outside of the state of Tennessee, the investigator must consult Legal Counsel about which individuals are "legally authorized representatives" when the research is conducted in that jurisdiction. Researchers must submit a copy of this legal opinion to the IRB.

Investigators must obtain a copy of the court order if a court appointed conservator or guardian gives consent. Investigators must obtain a copy of the DPAHC if person named in the patient's Durable Power of Attorney for Health Care (DPAHC) gives consent. In addition, if an individual identified to serve as the surrogate decision-maker for this patient gives consent, the investigator must document additional information evidencing the person's qualifications to serve as a surrogate. That information must include how long this person has lived with the patients, how long this person has known the patient and how often this person sees the patient, and any other evidence of the appropriateness of the selected surrogate.

## **Exculpatory Language**

Exculpatory language is prohibited. Informed consent, whether oral or written documents, may not contain any exculpatory language through which the subject 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, ETSU, VAMC or its agents from liability for negligence.

## **Retention of ICDs**

If the subject is under treatment, and a medical chart is maintained, an original copy of the signed consent document must be included with BOTH the patient's chart and the research records (HIPAA regulations apply). Additionally, a copy of the consent form must be given to the participant. (If electronic medical charts are used, a hard copy informed consent must be generated and maintained as per the above guidelines. Annotation will be made in the electronic medical record that the patient is a subject in a research protocol.) (See VA section for VA rules)

## **Deferred Consent or Ratification is Not Permitted (e.g., an investigator signs the ICD on behalf of a potential subject)**

Informed consent procedures which provide for other than legally effective, prospectively obtained consent fail to constitute informed consent under the Federal Regulations for the protection of human subjects. Therefore, waiving informed consent using a method other than those described herein and specified in the Federal Regulations is a violation of this policy.

## **Telephone Consenting is Not Recommended**

For non-VA studies, an investigator may, however, conduct a preliminary telephone interview to query a participant's interest in possibly participating in the research. If initial contact with prospective study subjects is to be made by telephone, a script of the phone contact is to be reviewed and approved by the IRB prior to use. Similarly if initial contact is to be made by mail, the content of the mailing script and list must be reviewed and approved by the IRB prior to initiation. Following the telephone interview, and under certain circumstances (to be determined by the IRB with evidence of need), the investigator can fax an IRB approved informed consent document to the participant for his or her review. Documentation of this process is critical. The signature page must be witnessed by an individual known to the IRB or notarized, and reflect both the date and time of each signature. Enrollment may begin once the Principal Investigator receives a copy of the signed and notarized consent document. The original document must be immediately (within 24 hours) forwarded to the study file or patient record as appropriate, to be placed in the patients medical record upon discharge. The date and time that the consent document (signed, notarized original copy) was entered into the patient chart must additionally be noted in the progress notes.

For VA studies, during the recruitment process, researchers must make initial contacts with veterans in person and/or by letter prior to any telephone contact and provide a telephone number or other means the veterans can use to verify the validity of the study (One source of information is <http://www.clinicaltrials.gov>).

## **Requiring Signature of Witness**

The VA policy is that the VA form 10-1086 must be signed and dated by a witness whose role is to witness the subject's or the subject's legally authorized representative's signature. The institution and the IRB reserve the right to require the signature of a witness on informed consent documents, as a matter of policy, under certain situations. Both the institution and the IRB have the authority to require protections for human subjects that exceed the minimum standards required under federal or state regulations. If the sponsor or the IRB require a witness to the consent process who also witnesses the signature, a note to that effect must be added to the consent document under the witness's signature line.

## **HIPAA**

When the HIPAA Authorization is embedded in the body of the ICD the IRB shall be responsible for reviewing both the content of the Authorization and its appropriateness to the research. When the HIPAA Authorization is attached to the ICD as an addendum (preferred), the IRB Chair, designee of the Chair, or the IRB Coordinator shall be responsible for the review.

## **Children**

For participants < than 18 years of age, their parents or legal guardian are the legally authorized representative who may grant permission for their participation in research. When research is conducted in the state of Tennessee, children are all individuals under under the age of 18 without exception.

According to the Tennessee Department of Children Services (DCS), applicable policies by virtue of the court order granting DCS legal custody of certain children (e.g., foster children) that department is the agency that is authorized to grant permission for participation in research in their custody. The decision of whether to grant permission for research is made on a case-by-case basis by DCS. In such cases the PI must obtain a copy of the court order from DCS. The case manager (including the case manager's supervisor(s) or Regional Administrators' designee (s), the foster parent, and the contract agency caseworker are authorized by DCS to sign consent for routine medical care.

DCS is authorized under Tennessee State law to consent to health care for the child, and therefore can serve as a guardian as defined in Subpart D.

## **Applicable State Laws Regarding Reporting Requirements**

**I. Mandatory Reporting of Abuse.** Any person who has knowledge of or is called upon to render aid to any child who is suffering from or has sustained any wound, injury, disability, or physical or mental condition is required to report the harm immediately by telephone to the:

- ⇒ Judge having juvenile jurisdiction over the child;
  - ⇒ County office of the department;
  - ⇒ Sheriff of the county where the child resides; or
  - ⇒ Chief law enforcement official of the municipality where the child resides.
- ⇒ The report will include (to the extent known) the name, address, and age of the child, the name address of the person responsible for the care of the child, and the facts requiring the report.

**II. Mandatory Reporting of Sexually Transmitted Disease.** Every physician or other person who makes a diagnosis of, treats or prescribes for a case of sexually transmitted disease designated as reportable is required to report the case immediately to the Department of Health. Reports include the name, address, age, sex, race, stage of disease, treatment, and control of the disease.

- ⇒ Children 13 years of age or younger must be reported to the Department of Health.
- ⇒ Reporting is required for children where sexual abuse is suspected regardless of injury to the Department of Health and the Department of Health will notify the Department of Children's Services.

**III. Mandatory Reporting of Cancer.** All laboratories, hospitals, facilities and practitioners are required to report to the Department of Health within 6 months of diagnosis any cancer in an individual if making the initial diagnosis. The report includes the diagnosis, occupation, family history and personal habits of the person diagnosed with cancer. Because of these laws, IRB members must evaluate studies to determine whether disclosure of the implications of the laws is required for legally effective informed consent. Because of these laws, investigators must ensure that the consent process provides participants with accurate information concerning required reporting. Investigators are also responsible for compliance with these regulations.

### **Payment of Investigators**

It is recommended that notice be provided in the Informed Consent Document that is signed and given to the subject if the investigator is to receive payment for enrollment of subjects. When a sponsor requires disclosure, the IRB will accept the statement if the provisions of 45 CFR 46.116 (d)(1)-(4) exist and are documented in writing by the sponsor and/or investigator.

### **Waiver of Informed Consent**

DHHS provides for waiving or altering elements of informed consent under certain conditions [§.116(c)-(f)]. FDA has no such provisions because the types of studies that would qualify for waiver or alteration are either not regulated by FDA or are covered by the Emergency Treatment provision of FDA Regulation 21 CFR 50.23.

### **Waiver of informed consent can not be given when research is subject to FDA regulation.**

The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirement to obtain informed consent provided one of the following sets of conditions exists and is documented:

- ⇒ 45 CFR 46.116(c) (Must meet one of the following criteria from section 1 as well as criteria number 2) (**not applicable to research subject to FDA regulation**)
  1. 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 at least one of the following (a) public benefit or service programs; (b) procedures for obtaining benefits or services under these programs; (c) possible changes in or alternatives to those programs or procedures; or (d) possible changes in methods or levels of payment for benefits or services under those programs

**AND**

  2. the research could not practicably be carried out without the waiver or alteration.

⇒ 45 CFR 46.116(d) (Must meet all four criteria detailed below) (**not applicable to research subject to FDA regulation**)

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

A waiver of parental permission (or student consent if the student is an adult) may not be granted if the study involves funding from the Department of Education and the study involves a survey, analysis, or evaluation that reveals information concerning the following categories:

- (1) political affiliations or beliefs of the student or the student's parent;
- (2) mental or psychological problems of the student or the student's family;
- (3) sex behavior or attitudes;
- (4) illegal, anti-social, self-incriminating, or demeaning behavior;
- (5) critical appraisals of other individuals with whom respondents have close family relationships;
- (6) legally recognized privileged or analogous relationships, such as those of lawyers, physicians, and ministers;
- (7) religious practices, affiliations, or beliefs of the student or student's parent; or
- (8) income (other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under such program),

In addition, all instructional materials, including teacher's manuals, films, tapes, or other supplementary material which will be used in connection with any survey, analysis, or evaluation as part of any applicable program shall be available for inspection by the parents or guardians of the children.

### **Waiver of Documentation of Informed Consent**

Under certain conditions, the IRB can waive the requirement that the participant sign the consent form. However, waiver of documentation of informed consent does not constitute waiver of informed consent. The IRB reviews the written description of the information that will be provided to participants. The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all participants if it finds either (46 CFR 117(c):

1. That the only record linking the subject and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality. Each participant will be asked whether the subject wants documentation linking the subject with the research, and the participant's wishes will govern. (**not applicable to research subject to FDA regulation**)

OR

2. that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases where the documentation requirement for informed consent is waived, the IRB requires the investigator to provide participants with a written statement regarding the research.

## **Confidentiality/ Anonymity**

### **Legal Challenges and Confidentiality**

In the informed consent procedure, subjects are often given assurances that the confidentiality of records identifying the subjects will be maintained.

Loss of confidentiality may occur however, when a court orders that research files or information be submitted as evidence in a legal matter. The court decides who has access to the files and what information may be required to be provided.

Unless there are no identifiers on project materials and subject lists are not maintained, complete confidentiality or records identifying the subjects may be assured only to the extent that disclosure is not compelled by court order. When FDA regulated products are being studied, the informed consent document should state that the FDA may review and copy the subject's medical records and, if necessary, obtain the identity of the subject.

### **Inadvertent Disclosure**

Security in storage, limitation of access, and coding constitute the best means to minimize risk of inadvertent disclosure to unauthorized parties. Measures to prevent this problem should be described in applications for studies in which the data collected is sensitive.

### **Certificate of Confidentiality**

In instances when the nature of the research is extremely sensitive and where the protection is judged necessary to achieve the research objectives, a *Certificate of Confidentiality* may be granted by the Director of the Office for Human Research Protections (OHRP).

Research can be considered sensitive if it involves the collection of information in any of the following categories:

- a. Information relating to sexual attitudes, preferences, or practices;
- b. Information relating to the use of alcohol, drugs, or other addictive products
- c. Information pertaining to illegal conduct;
- d. Information that if released could reasonably be damaging to an individual's financial standing, employability, or reputation within the community;
- e. Information that would normally be recorded in a patient's medical record, and the disclosure of which could reasonably lead to social stigmatization or discrimination;
- f. Information pertaining to an individual's psychological well-being or mental health.

This document is not a substitute for the Informed Consent form, but instead protects the confidentiality of data collected by the authorized individual by keeping all identifiable information away from all persons not associated with the research. If approved (by OHRP), once a Certificate of Confidentiality is granted, the authorized individual cannot be compelled to release any identifiable information. This authority is in a new subsection [301(d)] of the Public Health Service Act. It reads as follows:

The Secretary (DHHS) may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, including research on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals. [(Public Health Service Act, S 301(d), 42 U.S.C. §241(d), as added by Pub. L. No. 100-607, S 163 (November 4, 1988)].

*Certificates of Confidentiality* can be obtained by writing to the Director of the Office for Human Research Protections (OHRP), Department of Health and Human Services, 6100 Executive Boulevard, Suite 3B01, MSC-7507, Rockville, MD 20892-7507.

## Consistency of consent with contract

For initial studies with an associated contract, the PI is responsible for submitting a copy of the contract or at minimum, a copy of any contract pages that reference provisions for medical care or other care and services for research-related injury. ETSU's Sponsored Programs contract staff are responsible for verifying that there is consistency for provisions of medical care or other care or services for research-related injury between the consent document and contract.

If verification of consistency between the consent document and the contractual language regarding provisions of medical care or other care or services for research-related injury is not available at the time of initial review, a final IRB approval will not be issued until this verification by Sponsored programs is obtained.

Principal Investigators are responsible for verifying consistency of language between the contract and the consent document before submission to the IRB. If revisions are subsequently made to the sections of the contract pertaining to provisions of medical care or other care or services for research-related injury, the PI is responsible for submitting the revisions to the IRB. The IRB Coordinator will forward to Sponsored Programs contract staff for verification of consistency.

This policy applies to all studies with an associated contract.

## CHAPTER 6 - Amendments

It is the policy of both the ETSU IRB and the ETSU/VA IRB to review all requests for modifications to any previously approved research study (including exempt studies) to determine if the change will alter the risk/benefit ratio of the study. A complete description of the modification must be received prior to review. Modifications may include, but are not limited to, protocol amendments, changes in the number of subjects, changes in the informed consent, etc. All requested changes in the conduct of a study and/or changes to study documents must be approved by the IRB prior to implementation of that modification. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects [21 CFR 56.108(a) (4)]. In such a case, the IRB will be promptly informed of the change following its implementation (within 10 working days) and will review the change to determine that it is consistent with ensuring the subject's continued welfare. IRB members with a conflict of interest may provide information requested by the IRB, but may not participate in the deliberation or vote of the IRB on the involved modification.

### **Modifications Requested by Sponsor**

If the modification is requested by the sponsor, a copy of any pertinent correspondence from the sponsor must be submitted with the Modification Request Form. In addition, investigators must submit any proposed revised documents with the Modification Request Form.

### **Reconsenting/Notification of Participants**

If the modification warrants changes to the informed consent document, the investigator must address whether the information needs to be communicated to currently or previously enrolled participants, and if so, how it will be communicated. This may be accomplished by using an addendum to the initial ICD or by re-consenting the subject using the modified ICD. While the investigator is responsible for making the initial decision regarding any necessary document changes, the IRB will make the final determination of whether the modification requires a change to the ICD or other study documents. The IRB will also make the final determination of the necessity of re-consenting of currently enrolled participants or notification of participants who have completed research interventions.

### **Minor Modifications**

The initial determination as to whether a modification alters risks to the participants is made by the Principal Investigator. The modification is received by the Coordinator and presented it to the Chair for his/her review. The Chair is responsible for evaluating the change in procedures and risks, and determining whether full IRB review of the modification is necessary.

Proposed changes for previously approved research that are classified as minor modifications may be reviewed and approved in an expedited manner by the IRB Chair or, in the case of the Chair's absence or conflict of interest, his/her Designee. The designee should be one or more experienced reviewers designated by the chairperson from among the IRB membership. Examples of minor modifications may include, but are not limited to, the following:

1. Administrative changes, such as correction of typographical error(s)
2. Revision of phone number(s)

## **Non-Minor Modifications**

When a modification is determined to be non-minor, the Chair or his/her designee serves as a primary reviewer. The IRB Committee receives a synopsis of the primary reviewer's findings at the convened meeting. The IRB must review and approve changes at a convened meeting\* before changes can be implemented (\*meeting at which a majority of the members are present, including at least one member whose primary concerns are non-scientific). At the Chair's discretion, the Principal Investigator may be required to present the non-minor modification to the convened board.

Examples of non-minor modifications may include, but are not limited to, the following:

- ⇒ Change in protocol procedures, such as increasing the number of times a test is performed or adding additional procedures
- ⇒ Deletion or decrease in tests performed as part of safety evaluations
- ⇒ The addition of serious unexpected adverse events or other significant risks to the ICD
- ⇒ Changes, which, in the opinion of the IRB Chair or his/her Designee, do not meet the definition of a minor modification
- ⇒ Any change that increases the risk of the study

## **Exempt Research**

Any changes in an exempt study must be submitted to the IRB for approval prior to initiation of the change. The IRB Chair will determine if the modification renders the study ineligible for continuing exempt status; and if so, the modification will not be approved. The investigator will be notified in writing that he may withdraw the modification request and continue the study as previously determined to qualify under exemption guidelines or submit the study for appropriate review and approval through an expedited or full board review.

## **VA Studies**

Modifications must also be submitted to the VA R&D Office, if the study involves VA patients, VA staff, VA resources, time or equipment. Any change in authorized prescribers of the investigational drug requires the submission of a revised 10-9012.

## **Changes in Study Sites or Investigators**

Changes in study sites, investigators or revisions in study staff must also be reported to the IRB. These may require a cover letter, a revised Form 103, or, as applicable, a revised protocol. In the case of a change in the principal investigator, if at all possible, the letter should be signed by the investigator who holds the approval. The newly assigned investigator of a full review study however, must show proof of having obtained required education, submit a current CV for the purpose of assessment of qualifications, and attend a convened IRB meeting. The change will be noted in the minutes.

## CHAPTER 7 - CONTINUING REVIEW

The Department of Health and Human Services (DHHS), the Food and Drug Administration, East Tennessee State University and the James H. Quillen Veterans Affairs Medical Center, under the DHHS Regulations, Title 45 Code of Federal Regulations Part 46 (45 CFR 46), require at 46.109 (e), that “an IRB shall conduct continuing review covered by this policy at intervals appropriate to the degree of risk, but not less than once per year...” of all projects involving human subjects. The policy of both the East Tennessee State University Campus Institutional Review Board (ETSU IRB) and the East Tennessee State University/ Veterans Institutional Review Board (ETSU/VA IRB) is to conduct continuing review of all research proposals at intervals appropriate to the degree of risk, but not less than once per year [21 CFR 56.108(a)(1), 56.109(f) and 45 CFR 46.109(e)]. Continuing review is substantive and meaningful, and of sufficient depth and frequency to ensure the continued protection of the rights and welfare of research participants. No IRB member may participate in the continuing review of any protocol in which they have a conflicting interest, except to provide information requested by the IRB.

### Procedures for Continuing Review

- ⇒ **As a courtesy**, the IRB Coordinator will forward a letter to the Principal Investigator (PI) requesting submission of a completed Application for Continuing Review. The template letter will clearly state the protocol number, Study title, current approval date, study status at last review, the date of expiration of approval, scheduled meeting date, the version date of latest approved informed consent, and the deadline for submission of completed packet.
- ⇒ The letter will be forwarded approximately 4 weeks prior to the submission deadline, which will be approximately 8 weeks prior to the project expiration. If a response is not received by the deadline, a Warning Letter is faxed and mailed to the PI and the Department/Chair.

### Investigator Responsibilities

It is the investigator's responsibility to initiate an appropriate response, allowing sufficient time for the review and re-approval process to be completed before the current approval expires. Prior to the identified submission deadline, the PI will submit the following in response to the Request Letter for Continuing Review Application:

- ⇒ Original, completed Continuing Review/Study Closure Application (Form 107) (available at website: [www.etsu.edu/irb](http://www.etsu.edu/irb), Forms link) The Investigator's original signature on the Form 107 indicates his/her assurance that the information presented for continuing review is accurate and current.
- ⇒ Any required attachments as identified on the Continuing Review/ Study Closure Application, including but not limited to applicable brief descriptions of summary events/reports
- ⇒ A copy of the current, IRB stamped, approved informed consent, (this will provide a verification that the investigator is using the current approved version)

- ⇒ Two clean, unstamped copies of the identical informed consent to be stamped with the new continuing review approval dates. However, if a modification that changes the ICD is being submitted at the time of Continuing Review, the investigator must submit revised ICDS as indicated in the Modification Policy.

The Investigator ensures that the Continuing Review/Study Closure Application (Form 107) is complete, answering all items as noted below and attaching necessary summary descriptive information:

- ⇒ Project status, IND information, population involved, enrollment update, including total number of consented participants, including screen failures/withdrawals, total multi-center enrollment if applicable, number of subjects consented by local PI since previous IRB review, number of male/female subjects, and number of participant withdrawals, any recruitment problems
- ⇒ Summary of project activities that have occurred since previous IRB review, including
  - ⇒ Adverse events summary
  - ⇒ Any Data and Safety Monitoring Reports
  - ⇒ Any unanticipated problems involving risks to participants or others
  - ⇒ Any protocol changes (amendments or modifications)
  - ⇒ Any audits
  - ⇒ Any change in risk/benefit ratio
  - ⇒ Any complaints received from participants
  - ⇒ Any participant withdrawals and reasons for withdrawals
  - ⇒ Any interim findings
  - ⇒ Any progress reports
  - ⇒ Any multi-center reports, if applicable
  - ⇒ Any recent relevant literature
  - ⇒ Any protocol violations or deviations
  - ⇒ Any other relevant information, especially information about risk

**Study Expiration:** If study approval expires, the Investigator will cease all research activities as instructed in the Expiration Letter. Upon receipt of the Expiration Letter, the investigator will immediately notify the IRB Chair of any subjects currently active in the project who could be harmfully affected by expiration of the research. If follow-up of subjects for safety reasons is permitted/required by the IRB, the subjects will be so informed and any adverse events/outcomes should be reported to the IRB and sponsor.

## **NO Grace Period**

Per regulations, there is **no** grace period that allows the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur on or before the date when IRB approval expires. If any activity occurs or continues after the expiration date, the investigator is deemed to be out of compliance with both federal regulations and ETSU/VA policies.

The IRB may restrict, require modifications, or terminate a research project based on continuing review by the IRB Committee. All studies in which the IRB requests changes to current documents are assigned a pending status. IRB approval is not given until the requested changes are received and approved. **The expiration period is not extended.**

If continuing review and re-approval fails to occur by the continuing date specified by the IRB, all research activities must **stop**, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. Such expiration of IRB approval does not need to be reported to OHRP as a suspension of IRB approval under DHHS regulations.

If the IRB does not re-approve the research by the expiration date, the IRB approval expires. The PI, upon receipt of expiration letter, must immediately submit to the Chair a list of research participants that could be harmfully affected by expiration of the research.

## **Exempt Studies:**

Studies that have been determined to meet exempt status do not undergo continuing review unless a change in the study renders it ineligible for exempt status per federal guidelines. Investigators are informed in the exempt status letter to inform the IRB of any change in the project prior to its implementation, and reclassification under expedited or full review would be determined at that time by the IRB Chair.

## **Approval Criteria**

Approval, both initial and continuing, must meet HHS regulations at 45 CFR 46.111, including determinations by the IRB regarding risks, potential benefits, informed consent and participant safeguards. Criteria for both initial and continuing review approval are the same and therefore, IRB continuing review must include a determination by the IRB that

- ⇒ risks to subjects continue to be minimized
- ⇒ risks to subjects continue to be reasonable in relation to anticipated benefits and the importance of knowledge
- ⇒ selection of subjects continues to be equitable
- ⇒ informed consent continues to be adequate, and appropriately obtained and documented;
- ⇒ where appropriate, the research plan continues to make adequate provision for monitoring the data collected to ensure the safety of subjects;
- ⇒ there continue to be adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data
- ⇒ appropriate safeguards continue to be included to protect vulnerable participants
- ⇒ current risk/benefit analysis based on study results

If interim changes in IRB policy have occurred such that the proposal submitted for continuing review would not be approved if the same study were an initial submission, the IRB does not approve the continuing review of that protocol.

## **Changes/New Information**

The IRB is also responsible for ensuring that changes in approved research are promptly reported to, and approved by, the IRB [21 CFR 56.108(a)(3-4)]. Continuing review will include an IRB determination of whether new information or unanticipated risks have been discovered since the previous IRB review. Based on new information or unanticipated risk, the IRB has the authority to reconsider its approval, require modifications to the study, and/or revise the continuing review timetable. Any significant new findings which may relate to the subjects' willingness to continue participation should be provided to the subjects in accordance with 21 CFR 50.25.

## **Suspending/Terminating**

The IRB is also responsible for suspending or terminating approval of research that is not being conducted in accordance with the IRB's requirements [21 CFR 56.108(b)(2) and 56.113]. The IRB, by regulation, has not only the authority but also the responsibility for taking appropriate steps including termination or suspension of approval of research that is not being conducted in accordance with the IRB's requirements.

## **Informed Consent**

IRB continuing review will also include evaluation of the informed consent document currently in use. The currently approved informed consent, as well as any proposed informed consent document, will be reviewed to determine if the information provided continues to be accurate and complete, and to determine if any new information needs to be added. The informed consent document will also be reviewed to ensure that any significant new findings that may relate to the subject's willingness to continue participation are provided to the subject in accordance with HHS regulations at 45 CFR 46.116(b)(5). Review of the informed consent document will take place not only at continuing review, but at other times when new information becomes available that needs to be communicated to participants.

## **Study Closure**

The IRB requires that all investigators notify the IRB Coordinator, and VA R&D if applicable, in writing by using IRB Form 107, when a study is completed.

## CHAPTER 8 - Vulnerable Population

The ETSU and ETSU/VA IRB will consider certain groups of human subjects to be particularly vulnerable to coercion or undue influence in a research setting, to include children (also indirectly an infant, if mother nursing the infant is a subject of research), fetuses, pregnant women, mentally disabled (cognitively impaired) persons, prisoners, and economically or educationally disadvantaged persons. In reviewing research projects, the IRB will scrutinize those involving these vulnerable groups, to ascertain that their use is adequately justified, and additional safeguards are implemented to minimize risks unique to each group.

### Research Involving the Cognitively Impaired

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

1. Only incompetent persons or persons with impaired decision making capacity are suitable as research participants. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired-decision making capacity as participants. Incompetent persons or persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.
2. The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.
3. Procedures have been devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity. Health care agents (appointed under Durable Power of Attorney for Health Care (DPAHC)) and next-of-kin, or guardians, must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.
4. The IRB must make a determination in writing of each of these criteria. Investigators must submit a form 142.
5. Both investigators and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For subjects with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary.
6. Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be

forced or coerced to participate.

Surrogate consent may be requested and accepted only when the prospective research participant is incompetent or has an impaired decision-making capacity, as determined and documented in the person's record. For VA studies, this must be documented in the person's medical record in a signed and dated progress note. The determination must be made in accordance with the following requirements. Refer to Informed Consent Policy for information about surrogate consenting.

A. The practitioner may determine after appropriate medical evaluation that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time. For VA studies, this determination must be made in consultation with the chief of service, or COS.

B. For VA studies only, consultation with a psychiatrist or licensed psychologist must be obtained when the determination that the prospective research subject lacks decision-making capacity is based on a diagnosis of mental illness.

C. The participant's surrogate must be provided all information that normally would be provided to a participant.

D. If feasible, the practitioner must explain the proposed research to the prospective research subject even when the surrogate gives consent. Under no circumstances may a subject be forced or coerced to participate in a research study.

## **Waiver of Assent**

The IRB may waive the requirement for assent of the subject when:

- ⇒ The capability of some or all of the subjects is so limited that they cannot reasonably be consulted;
- ⇒ In determining whether subjects are capable of assent, the IRB shall take into account the maturity, psychological state and physical state of the subjects involved.
- ⇒ This judgment may be made for all subjects to be involved in research under a particular protocol, or for each subject, as the IRB deems appropriate.
- ⇒ 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 subject and is available only in the context of the research; or
- ⇒ IRB determines that the assent may be waived according to the same criteria by which consent may be waived.

If subjects enrolled in the research develop the capacity to provide informed consent, the IRB may require consent of the subject in accordance with 45 CFR 46.116. When the IRB determines that assent is required, assent shall be documented by having the subject sign and personally date the written informed consent.

## **Children**

Investigators must submit a completed Form 140 if the research proposal involves minors. Please note that VA studies may not involve children.

## **Definitions**

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

“Assent” means a child’s affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. In determining whether children are capable of assenting, the investigator and the IRB must take into account the ages, maturity, and psychological state of the children involved [§.46.408(a)].

“Permission” means the agreement of parent(s) or guardian to the participation of their child or ward in research.

“Guardian” means an individual who is authorized under applicable State or Local law to give permission on behalf of a child to general medical care.

“Emancipated Minor” means a legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law, but who are entitled to treatment as if they had by virtue of assuming adult responsibilities, such as self-support, marriage or procreation. NOTE: In the state of Tennessee, the Age of Majority is 18 years of age.

“Minimal Risk” means where the probability and magnitude of harm or discomfort anticipated in the proposed 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.

## **Assessment of Risks, Benefits**

The IRB, when reviewing research involving children as participants, considers the risks, benefits, and discomforts in the proposed research and assesses their justification in light of the expected benefits. When assessing the risks and benefits, the IRB weighs the circumstances of the children under study, the magnitude of risks that may accrue from the research, and the potential benefits to the child or to society. The assessment of the probability and magnitude of the risk may be different in sick children and may vary depending on the disease the child may have. When assessing possible benefits, the IRB also considers the variability in health statuses, taking into account the current health status and the likelihood of progression to a worsened state without the research intervention.

Federal regulations require the IRB to classify research involving children into one of four categories and to document discussion of the risks and benefits of the research study. Those four categories of research are as follows:

1. Research not involving greater than minimal risk (45 CFR 46.404): The IRB may approve research involving children and not involving greater than minimal risk, provided that the IRB finds and documents that:
  - No greater than minimal risk to children is presented; and
  - Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (45 CFR 46.405): The IRB may approve research involving children in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual participant, or by a monitoring procedure that is likely to contribute to the participant's well-being, only if the IRB finds that:
  - The risk is justified by the anticipated benefit to the participant;
  - The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches; and
  - Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.
3. Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition (45 CFR 46.406): The IRB may approve research involving children in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual participant, or by a monitoring procedure that is not likely to contribute to the participant's well-being, only if the IRB finds that:
  - 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 that is of vital importance for the understanding or amelioration of disorder, or condition; and
  - Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.

4. If an IRB does not believe that research within the scope described in §§50.1 and 56.101 of this chapter and involving children as participants meets the requirements of §50.51, §50.52, or §50.53, the research may proceed only if: [45 CFR §46.407] [21 CFR §50.54]
- The IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.
  - The agency head, 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, determines either:
    - ◇ That the research in fact satisfies the conditions of 45 CFR §46.404, §46.405, or §46.406 {FDA: 21 CFR §50.51, §50.52, or §50.53}, as applicable, or
    - ◇ That the following conditions are met:
      - ◆ The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.
      - ◆ The research will be conducted in accordance with sound ethical principles.
      - ◆ Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 45 CFR §46.408 {FDA: 21 CFR §50.55}.

## **Consent and Assent**

Regulations require that the IRB determine that adequate provisions are made for obtaining and documenting the assent of the children, when in the judgment of the IRB, the children are capable of providing assent. In determining whether children are capable of assent, the IRB shall take into account the age, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in the research under a particular protocol, or for each child, as the IRB deems appropriate. When the IRB determines that assent is required, it will also determine whether and how assent must be documented.

## **Waiver of Assent**

The IRB may waive the requirement for assent of some or all of the children when:

- ⇒ The capability of some or all of the children is so limited that they cannot reasonably be consulted **OR**
- ⇒ 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

Even where the IRB determines that the participants are capable of assenting, the IRB may still waive the assent requirement if it finds and documents that:

- ⇒ The research involves no more than minimal risk to the participants;
- ⇒ The waiver will not adversely affect the rights and welfare of the participants;
- ⇒ The research could not practicably be carried out without the waiver; and
- ⇒ Whenever appropriate, the participants will be provided with additional pertinent information after participation

In addition, the IRB shall require the permission of each child's parents or guardian.

Only the parents may grant permission for their child's participation in research. Assent is to sought from the child only after permission has been obtained from the parent(s). Grandparents and other relatives may not grant permission unless they have been granted formal custody of the child by a court. In such cases, the PI must obtain a copy of the court order as evidence of that person's authority.

When parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404 or 45 CFR 46.405 (categories 1 and 2 above—Research not involving greater than minimal risk and research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects). For research covered by 45 CFR 46.406 and 45 CFR 46.407, (greater than minimal risk and no direct benefit or otherwise unapprovable) and permission is to be obtained from parents, both parents must give their permission, 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.

Permission by parents or guardians will be documented appropriately

## **Wards of the state**

Children who are wards of the State or other agency, institution, or entity can be included in research approved under 45 CFR 46.406 (number three above) or 45 CFR.407 (number four above) only if such research is either 1) related to their status as wards or 2) be conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. In research approved under 45 CFR 46.406 (number three above) or 45 CFR.407 (number four above), the IRB must require appointment of an advocate for each child who is a ward. This advocate serves in addition to any other individual acting on behalf of the child as a guardian or *in loco parentis*. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

## **Research Involving Pregnant Women, Fetuses and Neonates**

It is the policy of the IRB to provide additional protections for pregnant women, fetuses and non-viable neonates involved in research. The IRB does not allow pregnant women, fetuses or non-viable neonates to be involved in research without specific approval of their involvement in the research (e.g., consultation with professionals in the field).

1. Research involving pregnant women or fetuses: The IRB may approve research involving pregnant women or, fetuses only if the IRB finds and documents that all of the following conditions are met:
  - ⇒ Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
  - ⇒ The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
  - ⇒ Any risk is the least possible for achieving the objectives of the research;
  - ⇒ If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of 45 CFR 46.
  - ⇒ If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A (DHHS) 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.
  - ⇒ Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
  - ⇒ For children as defined in 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of 45 CFR 46.
  - ⇒ No inducement, monetary or otherwise, will be offered to terminate a pregnancy.
  - ⇒ Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
  - ⇒ Individuals engaged in the research will have no part in determining the viability of a neonate.

In addition, for VA studies involving pregnant women, the following criteria must be met as well:

- ⇒ Adequate provision has been made to monitor the risks to the participants and the fetus.
- ⇒ Adequate consideration has been given to the manner in which potential participants are going to be selected, and that adequate provision has been made to monitor the informed consent process such as:
  - Overseeing the actual process by which individual consents are secured either by approving enrollment of each individual into the activity, or by verifying, perhaps through sampling, that approved procedures for enrollment into the activity are being followed; and
  - Monitoring the progress of the activity and intervening, as necessary, through steps such as visits to the activity site and continuing evaluations to determine if any unanticipated risks have arisen.

Also, for VA studies, activities related to pregnant women must not be undertaken unless the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal, and, in all cases, is the least possible risk for achieving the objectives of the activity. Individuals engaged in the activity will have no part introducing any procedural changes, for research purposes, into the procedures for terminating the pregnancy.

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

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

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

- ⇒ Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
- ⇒ Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate;
- ⇒ Individuals engaged in the research will have no part in determining the viability of a neonate.
- ⇒ The requirements of paragraph (b) or (c) of 45 CFR 46.205 have been met as applicable.

3. **Neonates of uncertain viability.** Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by subpart B unless the following additional criteria have been met:
  - ⇒ The IRB determines that:
    - The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
    - The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
    - The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, 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. **Nonviable neonates:** After delivery nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:
  - ⇒ Vital functions of the neonate will not be artificially maintained;
  - ⇒ The research will not terminate the heartbeat or respiration of the neonate;
  - ⇒ There will be no added risk to the neonate resulting from the research;
  - ⇒ The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
  - ⇒ The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of Sec. 46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).
5. **Viable neonates.** If a neonate is judged viable (i.e., likely to survive to the point of sustaining life independently, given the benefit of available medical therapy), it is then called an infant and should be treated as a child for purposes of research participation. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of 45 CFR 46.

## **Research involving, after delivery, the placenta, the dead fetus or fetal material**

1. Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities. Tennessee Code Annotated section 39-15-208 makes it unlawful for any person or entity to engage in the following activities without the prior knowledge and consent of the mother:
  - medical experiments,
  - research, or
  - taking of photographs upon an aborted fetus.

Additionally, no person or entity may offer or accept money or anything of value for an aborted fetus. Violations of these provisions are punishable as a Class E felony .

2. If information associated with material described in paragraph A of 45 CFR 46.206 is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of the regulations are applicable.

## **Human Fetal Tissue**

1. Human fetal tissue may be used only if the woman providing the tissue makes a statement, made in writing and signed by the woman, declaring that: [42 USC §498A(b)(1)]
  - ⇒ The woman donates the fetal tissue for use in research.
  - ⇒ The donation is made without any restriction regarding the identity of individuals who may be the recipients of transplantations of the tissue.
  - ⇒ The woman has not been informed of the identity of any such individuals
2. Human fetal tissue may be used only if the attending physician with respect to obtaining the tissue from the woman involved makes a statement, made in writing and signed by the physician, declaring that: [42 USC §498A(b)(2)]
  - ⇒ In the case of tissue obtained pursuant to an induced abortion:
    - The consent of the woman for the abortion was obtained prior to requesting or obtaining consent for a donation of the tissue for use in such research.
    - No alteration of the timing, method, or procedures used to terminate the pregnancy was made solely for the purposes of obtaining the tissue.
    - The abortion was performed in accordance with applicable State law.
  - ⇒ The tissue has been donated by the woman in accordance with 42 USC §498A(b)(1).
  - ⇒ Full disclosure has been provided to the woman with regard to:
    - Such physician's interest, if any, in the research to be conducted with the tissue.
    - Any known medical risks to the woman or risks to her privacy that might be associated with the donation of the tissue and that are in addition to risks of such type that are associated with the woman's medical care.

Human fetal tissue may be used only if the individual with the principal responsibility for conducting the research involved makes a statement, made in writing and signed by the individual, declaring that the individual: [42 USC §498A(c)]

- ⇒ Is aware that:
  - The tissue is human fetal tissue.
  - The tissue may have been obtained pursuant to a spontaneous or induced abortion or pursuant to a stillbirth.
  - The tissue was donated for research purposes.
- ⇒ Has provided such information to other individuals with responsibilities regarding the research;
- ⇒ Will require, prior to obtaining the consent of an individual to be a recipient of a transplantation of the tissue, written acknowledgment of receipt of such information by such recipient; and
- ⇒ Has had no part in any decisions as to the timing, method, or procedures used to terminate the pregnancy made solely for the purposes of the research.

**46.207: Research Not Otherwise Approvable Which Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Pregnant Women, Fetuses, or Neonates.**

The Secretary of the Department of Health and Human Services (DHHS) will conduct or fund research that the IRB does not believe meets the requirements of 45 CFR 46.204 or 45 CFR 46.205 only if:

- ⇒ The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates; and
- ⇒ The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the Federal Register, has determined either:
  - That the research, in fact, satisfies the conditions of §46.204, as applicable; or
  - The following:
    - ◇ The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates; and
    - ◇ The research will be conducted in accord with sound ethical principles; and
    - ◇ Informed consent will be obtained in accord with the informed consent provisions of 45 CFR 46 Subpart A and other applicable subparts of 45 CFR 46

## **Research Involving Prisoners**

The provisions of 45 CFR 46 Subpart C provide additional protections to biomedical and behavioral research involving prisoners as participants. These safeguards apply to research where any participant is or becomes a prisoner.

A prisoner is defined by HHS regulations at 45 CFR 46.303 as “any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.”

## **Required IRB Composition**

Whenever the IRB reviews a protocol in which a prisoner is a subject:

- ⇒ A majority of the IRB (exclusive of prisoner members or prisoner advocates) must have no association with the prison(s) involved, apart from their membership on the IRB;
- ⇒ At least one voting IRB member present at the meeting must be a prisoner, or a prisoner advocate /representative with appropriate background and experience to serve in that capacity.

These composition requirements must be met for all types of review of the protocol, including initial review, continuing review, review of protocol modifications, and review of unanticipated problems involving risks to participants.

## **Additional IRB Duties**

In addition to all other pertinent requirements, the IRB may approve research involving prisoners only if the IRB finds and documents that all of the following conditions are met:

1. The research under review represents one of the following categories of permissible research (45 CFR 46.306):
  - ⇒ Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk\* for prisoners and no more than inconvenience to the subjects;
  - ⇒ Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk for prisoners and no more than inconvenience to the subjects;
  - ⇒ 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); provided that the study may proceed only after the Secretary (through OHRP) has consulted with appropriate experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his intent to approve such research;\*\* or

- ⇒ Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary (through OHRP) has consulted with appropriate experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his intent to approve such research.\*\*

\* Note that the definition of minimal risk for prisoner at 45 CFR 46.303(d) differs from the definition of minimal risk for other research: For prisoner: the definition of 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.”

\*\* Refer to section C, Research Conducted or Supported by DHHS

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 subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the PI provides to the IRB justification in writing for following some other procedures, control subject must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
5. The information is presented in language which is understandable to the subject population;
6. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decision regarding parole; and each prisoner is clearly informed in advance that participation in the research will have no effect of his or her parole; and
7. Where the IRB finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual's sentences, and for informing participants of this fact

## **Research Conducted or Supported by DHHS**

For research conducted or supported by HHS to involve prisoners, the following two actions must occur:

- ⇒ The Institution engaged in the research must certify to the Secretary (through OHRP) that the IRB designated under its assurance of compliance has reviewed and approved the research under 45 CFR 46.305.
- ⇒ The Secretary (through OHRP) must determine that the proposed research falls within the categories of research permissible under 45 CFR 46.306(a)(2).

To fulfill these requirements, the IRB Staff will prepare and send to OHRP a certification letter stating:

- ⇒ The IRB (including name and address) has been constituted according to the regulations;
- ⇒ The IRB considered and made the required 7 findings set forth in 45 CFR 46.305;
- ⇒ The category of approval under 45 CFR 46.306 that permits this research to go forward with prisoners as human subjects;
- ⇒ Whether OHRP needs to consult with appropriate experts and publish a Federal Register Notice.

The certification letter will specifically identify the research protocol and any relevant HHS grant application or protocol. A copy of the research proposal, including the IRB-approved protocol, any relevant HHS grant application or proposal, any IRB application forms, and any other information requested by the IRB during initial IRB review, will be sent with the letter.

OHRP will determine which permissible category, if any, under which the proposed research qualifies. OHRP is responsible for consulting with experts and/or publishing in the Federal Register as appropriate with respect to paragraphs (iii) and (iv) of 45 CFR 46.306(a)(2).

Enrollment of prisoners into a DHHS conducted or supported research study may not begin until OHRP issues its approval in writing to the institution of behalf of the Secretary.

### **Participant Becoming Prisoner during Research**

If a research participant becomes a prisoner after enrollment in a research study, the Principal Investigator is responsible for notifying the IRB immediately. If the research proposal was not reviewed and approved by the IRB in accordance with the HHS regulations at 45 CFR 46, Subpart C, the PI must stop all research interactions with the participant, including obtaining identifiable private information, until the requirements of Subpart C have been satisfied by the IRB. OHRP allows one exception as follows: "In special circumstances in which the principal investigator asserts that it is in the best interest of the subject to remain in the research study while incarcerated, the IRB Chairperson may determine that the subject may continue to participate in the research until the requirements of subpart C are satisfied."

## **Additional Requirements**

In addition to IRB approval, investigators must obtain approval of the TDOC.

Tennessee Department of Corrections (TDOC) policy number 114.02 outlines the procedures for acquiring research approval within the department. These "Submittal instructions for research applicants" outline the guidelines as established by policy [114.02 (VI)(C)(1) for proposing and conducting research within TDOC facilities. The research process within the TDOC is consistent with American Correctional Association (ACA) standards referenced in *Standards for Adults Correctional Institutions, third edition*. Specific ACA standards pertaining to research activities within the Department of Correction include 3-4105, 3-4106, 3-4107, 3-4108, 3-4109, 3-4110 and 3-4373.

Because of this law, the IRB must ensure that all appropriate approvals are obtained.

Under 28 CFR 512, the Federal Bureau of Prisons places special restriction on research that takes place within the Bureau of Prisons. Additional requirements for prospective researchers to obtain approval to conduct research within the Federal Bureau are outlined.

Research involving prisoners must not be conducted by VA investigators while on official duty, or at VA-approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer.

## CHAPTER 9 - Recruitment and Selection of Participants

It is the policy of both the ETSU IRB and the ETSU/VA IRB that non-coercive methods must be used by investigators to recruit subjects. Procedures for enrolling subjects and compensation for subjects must minimize the possibility of coercion or undue influence. Direct advertising for research participants is considered to be the start of the informed consent and participant selection process.

**For VA Studies:** Non-veterans may be entered into VA approved research studies only when there are insufficient veterans available to complete the study. All regulations pertaining to the participation of veterans as research subjects pertain to non-veterans subjects enrolled in VA-approved research.

In VA studies, during the recruitment process, researchers must make initial contacts with veterans in person and/or by letter prior to any telephone contact and provide a telephone number or other means that veterans can use to verify the validity of the study (One source of information about clinical trials is <http://www.clinicaltrials.gov>). After recruitment and during the follow-up phase, VA researchers should begin phone calls by referring to previous contacts and the information provided on the informed consent document. In addition, for VA studies, researchers must restrict their telephone and other contacts with veterans to only those procedures and data elements outlined in IRB-approved protocols. **In these contacts, researchers must not request social security numbers.**

### Recruitment of Healthy Volunteers

Methods for subject recruitment must be addressed in the research narrative. When recruiting healthy volunteers, one of the following methods are recommended:

- ⇒ Use of public advertisement, (i.e., bulletin boards) including telephone number that a potential research subject may call to volunteer for the study.
- ⇒ Use of a letter briefly explaining the study and including a telephone number that a potential research subject may call to volunteer for the study.
- ⇒ Any alternative method (i.e., public advertisement, flyers, web site announcements) of contacting volunteers for research.

These items require IRB approval prior to use.

### Patient Recruitment

When a potential research subject is also a patient, i.e., a patient currently receiving treatment at one of the Institutions or a former patient who is to be recruited for a research study related to a medical problem, the following guidelines are recommended:

- ⇒ The IRB recognizes that often patients currently under treatment are to be recruited into a research study, and that the physician providing the care and the principal investigator are one and the same. The IRB further recognizes that in these situations a certain degree of unavoidable coercion exists, and the IRB will pay particular attention to the risk/benefit ratio

when reviewing such protocols.

- ⇒ Per HIPAA requirements outlined at 164.508, researchers should obtain written authorization from subjects before using or collecting protected health information (PHI). Authorization must be obtained in writing from prospective subjects. Protected health information: Individually identifiable health information excluding individually identifiable health information in (i) education records covered by the Family Educational Right and Privacy Act, as amended, 20 U.S.C. 1232g; and (ii) records described at 20 U.S.C. 1232g (a)(4)(B)(iv).
- ⇒ In those protocols where more than minimal risk is involved and the potential benefit to the subject is not direct, the IRB may elect to request that an uninvolved person participate in the patient selection process.
- ⇒ In those situations where the potential research subject is a patient under the care of a physician other than the investigator, it is recommended that the approval of that physician be obtained before the patient is contacted regarding the study (applicable for studies that involve treatment or other direct patient management decisions).
- ⇒ If former research subjects are to be contacted by either the PI or his/her appropriate designee, and asked to participate in follow-up, the individual should be contacted by letter (not telephone). In this instance, prior approval would be required from the IRB (Refer to minor modification requirements).

## **Research Advertising Materials Guidelines**

All advertisements, questionnaires, surveys, testing forms and/or introduction letters associated with the study and intended for subject use or view must be submitted to the IRB for approval.

Advertisements may not include the following:

- ⇒ The ad cannot state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol.
- ⇒ The ad cannot make claims, either explicitly or implicitly, that the drug, biologic, or device is safe or effective for the purposes under investigation.
- ⇒ The ad cannot make claims, either explicitly or implicitly, that the test article is known to be equivalent or superior to any other drug, biologic, or device.

- ⇒ The ad cannot use terms such as “new treatment,” “new medication,” or “new drug” without explaining that the test article is investigational.
- ⇒ The ad cannot promise free medical treatment when the intent is only to say participants will not be charged for taking part in the investigation.
- ⇒ The ad cannot include any exculpatory language.

Advertisements may include the following:

Advertisements to recruit participants should be limited to the information that prospective participants need to determine their eligibility and interest. When appropriately worded, the following items should be included in advertisements:

- ⇒ name and address of the Investigator;
- ⇒ purpose of the research;
- ⇒ criteria to be used to determine eligibility in a summary form;
- ⇒ location of the research (e.g., Vanderbilt);
- ⇒ a brief description of the study activities, when appropriate;
- ⇒ potential benefits, if any; and
- ⇒ name and phone number of the person to contact for further information.

Advertisements may also include a statement that participants will be paid, but should not emphasize the payment of the amount to be paid, by such means as larger or bold type.

The material should clearly state, “This is a Research Study,” or, when appropriate, “This Research Study involves the use of an Investigational Drug or Device.”

## **IRB Review**

The IRB Chair, or his/her designee, may approve advertisements that are easily compared to the approved Informed Consent document through the expedited mechanism. If the reviewer has any doubt or there are any complicating issues involved, the convened board will review the advertising.

The IRB will review the information contained in the advertisement and its method of communication to determine that participants are not coerced.

The IRB will review the final copy of all advertisements, including print advertisements and audio/video tape for broadcast. If an advertisement is to be broadcast, the IRB may review and approve the wording prior to taping. The approval of the final taped message prepared from the IRB-approved text can be given through expedited review.

## **Payment of Participants**

When the IRB evaluates the selection of participants, it considers the influence of payments to

participants. Payment to research participants is not considered a benefit but a recruitment incentive. The amount and schedule of all payments should be described in the IRB application at the time of initial review, including the amount of payment, and the proposed method and timing of disbursement. The IRB must review this information to assure that the amount, method, or timing of payment are not coercive and do not present undue influence. Credit for payment should accrue as the study progresses and not be contingent upon the participant completing the entire study. While the entire payment should not be dependent upon completion of the entire study, payment of a small proportion as an incentive for completion is acceptable, providing that such incentive is not coercive. The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce participants to stay in the study when they would otherwise have withdrawn.

Procedures for prorating payment should the participant withdraw should be considered when submitting the IRB application and informed consent documents. Unless it creates undue inconvenience or a coercive practice, payment to participants who withdraw from the study may be paid at the time the study would have been completed had they not withdrawn. For example, in a study lasting only a few days, it may be permissible to allow a single payment date at the end of the study, even to participants who withdraw before completion.

All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document and the narrative.

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.

**For VA Studies:** VA policy prohibits paying human subjects to participate in research when the research is integrated with a patient's medical care and when it makes no special demands on the patient beyond those of usual medical care.

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

- ⇒ When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice in affiliated non-VA institutions is to pay subjects in this situation
- ⇒ In multi-institutional studies, when human subjects at a collaborating non-VA institution are to be paid for the same participation in the same study at the same rate proposed
- ⇒ In other comparable situations in which, in the opinion of the IRB, payment of subjects is appropriate
- ⇒ When transportation expenses are incurred by the subject that would not be incurred in the normal course of receiving treatment and which are not reimbursed by any other mechanism.

## **Payment to Investigators**

A finder's fee is a payment from the investigator or sponsor to a person who refers a potential participant. Recruitment bonuses are payments from the sponsor to an investigator or organization based on the rate or timing of recruitment. Finder's fees, recruitment bonuses, and other financial incentives paid by a sponsor or investigator or others related to the recruitment of research subjects are prohibited. All payment by sponsors for research conducted by ETSU or VA employees must be made directly to the University, James H. Quillen VAMC, ETSU Research Foundation, or the James H. Quillen VA Research Foundation, as appropriate.

For physicians, the Tennessee Board of Medical Examiners deems certain recruitment incentives to be unethical and unprofessional conduct and could be subject to physician disciplinary action. In addition, the Federal anti-Kickback statute prohibits illegal remunerations.

ETSU bans all bonus payments for enrollment, including those that would be paid directly to the institution.

## **Students as Participants**

The Investigator should exercise particular discretion when recruiting students as research participants. Specifically, the Investigator should assure that consent for participation is sought only under circumstances which minimize the possibility of coercion or undue influence, and that genuinely equivalent alternatives to participation are available (e.g., alternate research activities, appropriate length term papers).

## CHAPTER 10 - Health Insurance Portability and Accountability Act (HIPAA)

**HIPAA** : The Health Insurance Portability and Accountability Act (HIPAA), also referred to as, The Privacy Rule, at 45 CFR parts 160 and 164, establishes a category of health information, defined as protected health information (PHI), which a covered entity may only use or disclose to others in certain circumstances and under certain conditions.

In general, the Privacy Rule requires an individual to provide his/her signed permission, known as an Authorization under section 164.508 of the Privacy Rule, before a covered entity can use or disclose the individual's PHI for research purposes.

### **Privacy Board**

Under certain circumstances, however, the Privacy Rule permits a covered entity to use or disclose PHI for research without an individual's Authorization. One way a covered entity can use or disclose PHI for research without an Authorization is by obtaining proper documentation of a waiver of the Authorization requirement by the IRB, or another type of review body, known as a Privacy Board. The ETSU/VA IRB shall serve as the Privacy Board.

### **Pre-screening Activities**

Pre-screening activities, without the use of an Authorization, are permitted under HIPAA [45 CFR 164.512(i)(1)(ii)]. Pre-screening activities involving prospective subjects, conducted to prepare a research protocol, or to enroll (or exclude) subjects from participation must be documented in the study file whether or not the subject meets the inclusion criteria or not. The Waiver of Informed Consent: Documentation of screening (pre-enrollment) activity only form, (available online) or a similar instrument may be used for this purpose. Note: VHA policy is more restrictive regarding Activities Preparatory to Research. Accessing patient records for recruitment into research requires prior IRB approval, waiver of authorization, even for a VA researcher's own patients.

### **Direct Identifiers (18 HIPAA Identifiers)**

When developing research protocols, the Investigator must take into consideration allowable use and disclosure of PHI under HIPAA. The following identifiers are considered links to a particular individual or data that could enable individual identification:

- ⇒ names;
- ⇒ geographic subdivisions smaller than a State, including street address, city, county, precinct, ZIP code, and their equivalent geocodes, except for the initial three digits of a ZIP code;
- ⇒ all elements of dates (except year) for dates directly related to an individual (e.g., date of birth, admission);
- ⇒ telephone numbers;
- ⇒ fax numbers;
- ⇒ electronic mail addresses;
- ⇒ social security numbers;

- ⇒ medical record numbers;
- ⇒ health plan beneficiary numbers;
- ⇒ account numbers;
- ⇒ certificate/license numbers;
- ⇒ vehicle identifiers and serial numbers, including license plate numbers;
- ⇒ device identifiers and serial numbers;
- ⇒ web universal locators (URL's);
- ⇒ internet protocol (IP) address numbers;
- ⇒ biometric identifiers, including finger and voiceprints;
- ⇒ full-face photographic image and any comparable images; and
- ⇒ any other unique identifying number, characteristic, or code.

## **IRB Authority**

The IRB has the authority to approve a waiver or an alteration of the Privacy Rule's Authorization requirement in addition to the traditional IRB authorities to protect research participants from risks under 45 CFR part 46 (Department of Health and Human Services (HHS) Regulations for the Protection of Human Subjects) 38 CFR 16, and 21 CFR parts 50 and 56 (Food and Drug Administration (FDA) Regulations on Protection of Human Subjects). Other Federal and State laws and regulations may impose other or additional restrictions and limitations on the use of health information for research that may not be waived or altered by an IRB (or Privacy Board) under the authority granted to it by the Privacy Rule. The IRB and the OPHRS shall enforce the mandates of the Privacy Rule pursuant to the requirements necessary for the protection of the subject and/or their protected health information as applicable to the research.

## **Training**

Training on the requirements imposed by the Privacy Act and other information regarding HIPAA, including guidance, forms and continuing education, will be made available to researchers online.

## Chapter 11 - Investigational Drugs, Agents, Biologics, and Devices

**Investigational Drugs/Investigational Biologics (Test Articles):** A new drug/agent or biologic that is used in a clinical investigation. The term investigational biologic also includes a biological product that is used *in vitro* for diagnostic purposes. Investigational drugs or biologics may include:

- A. Products that are not generally recognized as being safe and effective for any use under the conditions prescribed, recommended, or suggested by the FDA; or
- B. Products already approved by the FDA as safe and effective for specific indications that are being studied for new indications (or doses, strengths, or frequency).

Researchers who employ a test article classified by the Food and Drug Administration as an investigational new drug must comply with the FDA's IND regulations ([21 CFR 312](#)). The IND number assigned to the test article must be filed with the IRB when the application for review is submitted. See policy 33 for additional information about INDs.

### **Storage of Investigational Drugs/ Devices**

It is the policy of the ETSU/VA IRB that all investigational drugs, devices, drugs, or biologics used in human subject research be stored, handled and dispensed in accordance with governing regulations and institutional policy. It is the responsibility of the investigator to comply with all institutional, state, and federal regulations in regards to storage of investigational drugs, agents, or biologics.

### **VA / MSHA**

All research investigators conducting VA approved human subjects research protocols involving the use of pharmaceutical agents must be in compliance with all VHA policies/handbooks as they relate to obtaining, prescribing, and the storing of pharmaceuticals as well as addressing required record keeping. In addition, investigators using any controlled substances including Schedule II and III narcotics must be in full compliance with VHA Pharmacy Policies and Drug Enforcement Administration (DEA) Regulations. If the use of pharmaceuticals is covered under FDA Regulations, those regulations must be followed as well.

VA investigators must inform the Pharmacy Service through the use of VA Form 10-1223 that the IRB and Research and Development Committee approvals have been obtained. In addition, VA investigators must provide the Pharmacy Service with a signed copy of the VA Form 10-1086 to document each participant's consent to participate in the study. VA investigators are also responsible for informing the Chief, Pharmacy Service, and the Research and Development Committee when a study involving investigational drugs has been terminated.

In addition, studies conducted at Mountain States Health Alliance must follow all applicable MSHA policies.

Controlled substances may not be stored outside of the pharmacy department of the involved hospital.

## **PI Responsibilities Summary**

Protocols involving an Investigational Drug (IND) or Investigational Device (IDE) require compliance with the pertinent FDA and the DHHS regulations (21 CFR 50, 21 CFR 56, 21 CFR 312, 21 CFR 812, and 45 CFR 46).

The PI is responsible for assuring the IRB that investigational drugs and devices are stored in a secure and safe manner and that the storage and safety requirements are consistent with FDA, sponsor, and affiliated research institutions' storage requirements for drugs or devices being investigated. Whenever possible, the storage of drugs and biologics should be under the supervision of a registered pharmacist and stored in the pharmacy in a limited access, locked area. Devices should be stored according to manufacturer's specifications and maintained in a limited access area. Access to the test devices must be limited only to those authorized to use the devices.

The PI is responsible for ensuring that test articles (drugs, biologics, or devices) are controlled so that they are not used outside of a research study. An investigator shall administer the drug or device only to subjects under the PI's personal supervision or under the supervision of a sub-investigator responsible to the PI. The PI shall not supply the investigational drug or device to any person not authorized to receive it.

The protocol for the study should outline the security and storage plan for the test article(s) indicating that the plan meets the sponsor's storage and security requirements. The plan should include whether or not control will be through a hospital pharmacy and under the supervision of a registered pharmacist or held in a proper and secure storage area by the investigator. The protocol should detail how the test article is used in human subjects, indicate who may have access to the test article(s) and outline the accountability plan for the test article(s) to ensure that there is no unapproved access to or use of the test article(s).

PI responsibilities related to investigational drugs are outlined in Form 147. The form 147 is required for submission for investigational drug studies. PI responsibilities related to investigational devices are outlined in Form 148. The form 148 is required for submission for investigational device studies.

## **Additional Responsibilities for PI Acting as Sponsor**

If a PI is acting as the sponsor of research involving an investigational drug, the ETSU/VA IRB requires that the PI submit documentation that the proposed drug preparation has been reviewed and determined to be in compliance with Current Good Manufacturing Practices. In addition, when an PI is acting as the sponsor of research involving an investigational drug or device, the IRB requires that the PI review the reporting and record-keeping responsibilities as stated in 21 CFR 312 and 21 CFR 314 (for investigational drugs) or 21 CFR 812 and 21 CFR 814 (for investigational devices). (also see policy 33)

## **Medical Investigational Device Determinations**

A Significant Risk (SR) device study is defined [21 CFR 812.3(m)] as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. An NSR device investigation is one that does not meet the definition for a significant risk study.

NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the Institutional Review Board (IRB) regulations [21 CFR part 56] to identify certain studies that may be approved through an "expedited review" procedure. For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study [21 CFR part 50].

In reviewing studies involving medical devices, the Medical Campus ETSU/VA IRB will make two determinations:

- ⇒ Whether a device study represents a significant or non-significant risk; and
- ⇒ Whether the study should be approved.

These questions will be considered separately because the issues involved in making these decisions are quite different. Determining whether a device study poses a significant risk will be based solely on considerations of risk to subjects, while the IRB approval of the study is based on many factors. In determining whether a device study presents a significant or non-significant risk, both the risk of the device and the risk associated with the procedure for using the device (e.g., surgery for installing an implant) will be considered. The comparison of risks will provide the basis for whether or not the IRB will approve the research.

The initial assessment of whether or not a device study presents a non-significant risk (NSR) is made by the sponsor.

In addition to receiving a completed Form 103, narrative, informed consent, protocol and investigator's brochure (if available), the IRB must receive a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The IRB must also be informed whether other IRBs have reviewed the proposed study, and what determinations were made. In addition, the IRB must be informed of the FDA's assessment of the device's risk if such an assessment has been made. If the sponsor considers that a study is NSR, the sponsor must provide the IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The sponsor must provide the IRB with a risk assessment and the rationale used in making its risk determination [21 CFR 812.150(b)(10)].

For any device protocol considered (by FDA) to present significant risk, an IDE number will be required prior to submission to the ETSU/VA IRB for initial review. Conversely, if the FDA has made a determination of non-significant risk, than a copy of the determination letter received from FDA should be submitted with the protocol.

The IRB may also consult with FDA for its opinion. The IRB uses its expertise, information in the FDA regulations and guidelines, and the risk evaluation provided in the application to determine the risk category.

The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees with the sponsor's initial NSR assessment and approves the study, the study may begin without submission of an IDE application to FDA.

If the IRB disagrees and determines that the device is SR, the IRB informs the investigator and the sponsor in writing of this decision and its basis. The sponsor should notify FDA that an SR determination has been made. If the IRB determines that a device study is SR, the study **may not** begin until both the IRB and FDA approve the investigation. The study can be conducted as an SR investigation following FDA approval of an IDE application.

The risk determination should be based on the proposed use of a device in a investigation, and not on the device alone. In deciding if a study poses an SR, the IRB considers the nature of the harm that may result from use of the device. Studies where the potential harm to subjects could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure should be considered SR. Also, if the participant must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB considers the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

FDA has the ultimate decision in determining if a device study is SR or NSR.

If the investigator or organization is acting as the sponsor, the investigator or sponsor must follow all the additional regulatory requirements of sponsors. The IRB must evaluate whether the investigator knows how to follow the additional regulatory requirements of sponsors. In order to determine this evaluation, the IRB requires any investigator acting as the sponsor to read the FDA's "Responsibilities for Sponsors of Significant Risk Device Studies, Responsibilities for Sponsors of Non-Significant Risk Device Studies" , "Responsibilities for Investigators of Significant Risk Device Studies, Responsibilities for Investigators of Non-Significant Risk Device Studies" published on-line at <http://www.fda.gov/cdrh/devadvice/ide/print/responsibilities.html>. The IRB receives an signed attestation that the investigator/sponsor has read this document prior to issuing final study approval.

## CHAPTER 12 - Emergency Use of a Test Article

Emergency use is defined as the use of a test article (e.g., investigation drug, device or biologic) 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 for the use. The investigator is still required to obtain consent under these circumstances. The FDA exempts from IRB review the emergency use of a test article so long as the emergency use is reported to the IRB within five working days of its occurrence. Any subsequent use of the test article is subject to IRB review [21 CFR 50.23; 21 CFR 56.104(c)]. When emergency care involves investigational drugs, devices, or biologics, FDA requirements must be satisfied.

### Emergency Use

When an investigator identifies a need for emergency use of a test article, the following procedures must be implemented:

The IRB Chair or Vice Chair, or in their absence, a physician member of the IRB should be contacted. If the Chair is not an M.D., the Chair will make immediate contact with a qualified physician who is either 1) a member of the IRB, or 2) referred to the Chair by the member-physician as a qualified consulting-physician for concurrence on the emergency use approval. When the IRB Chair or Director receives a request for emergency use from a clinical investigator, the IRB Chair will examine each case, receive a collaborating statement from a physician associated with neither the patient nor the current attending physician (consult) supporting the emergency use and, upon request, assure the institution that the emergency use was justified. A copy of the FDA 1572 and approved IND or IDE will be requested of the investigator.

The ETSU/VA IRB Chair will also determine if the research is (or was) not a systematic investigation designed to develop or contribute to generalizable knowledge. The Chair will also determine that unless the criteria for the exception to the requirement for consent are (were) met, consent will be (or was) sought from each prospective participant or the participant's legally authorized representative, in accordance with and to the extent required by FDA regulations and will be appropriately documented, in accordance with and to the extent required by FDA regulations.

The investigator must report the emergency use of the test article to the IRB within five (5) working days. The ETSU/VA IRB Chair reviews this report and determines whether the circumstances of the emergency use complied with regulatory requirements. If the use meets the regulatory requirements, the investigator is notified of this determination by phone and in writing. If the use does not meet the regulatory requirements, the investigator is notified verbally and in writing that if the investigator goes forward with the use, the use will likely be in non-compliance with federal regulations.

## **Subsequent Use**

Any subsequent use of the test article is subject to full IRB review. Subsequent use means any use of the test article that occurs after its initial emergency use. Should the investigator or IRB anticipate a subsequent need to use the test article, a complete formal application must be made for IRB review at a convened meeting.

In some emergency circumstances, it may not be feasible to obtain informed consent prior to using the test article. The regulations [21 CFR 50.23(a)(1-4) and (b-c)], [116(d)(3) and 116(d)(4) (f)], therefore provide an exception for informed consent requirements for such situations. Except as stated below, in order for the exception to apply, both the investigator and a physician who is not otherwise participating in the clinical investigation must certify in writing all of the following: (1) the subject is confronted by a life-threatening situation necessitating use of the test article; (2) the subject is unable to provide effective consent; (3) there is insufficient time in which to obtain consent from the subject's legal representative; and (4) there is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is necessary to save the life of the subject and there is insufficient time to obtain the independent certification required before using the test article, the investigator is to make his or her own written determinations as outlined above, and within five (5) working days after the use of the test article, obtain the written review and evaluation of a physician who is not participating in the clinical investigation.

Documentation, in both instances, must be submitted to the IRB Coordinator within (5) working days after the use of the test article. The ETSU/VA IRB Chair reviews this report using the ETSU/VA Form 100 checklist and determines whether the use of the exception for informed consent requirements complied with regulatory requirements. If the use meets the regulatory requirements, the investigator is notified of this determination in writing. If the use does not meet the regulatory requirements, the use is handled according to the IRB non-compliance policy.

## CHAPTER 13 - Unanticipated Problems

### I. Pertinent Definitions:

**Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO):** Includes those events that (1) are not expected given the nature of the research procedures and the subject population being studied (2) suggest that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known or recognized and (3) are related or possibly related to the research.

Possibly related: there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected: unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document and given the characteristics of the subject population being studied

**Serious Adverse Event:** any adverse event that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For VA studies, an adverse event or problem in research is also considered serious when medical, surgical, behavioral, social, or other intervention is needed to prevent the outcomes above or to prevent substantive harm or damage (or risk of substantive harm or damage) to the safety, rights, or welfare of research subjects, research staff, or others.

## CHAPTER 13 - Unanticipated Problems

**Unexpected Adverse Event:** As defined by the FDA, any adverse event, the specificity or severity of which is not consistent with the current Investigator Brochure; or, if an Investigator Brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator Brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator Brochure only listed cerebral vascular accidents. **Clarification Note:** "Unexpected," as used in this definition, refers to an adverse event that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product and not listed in the Investigator's Brochure.

Unexpected adverse event: any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is NOT consistent with either (1) the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved consent document and (b) other relevant sources of information, such as product labeling and package inserts; or (2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

## **II. Summary Policy**

Federal regulations require the organization to ensure prompt reporting of “any unanticipated problems involving risk to subjects or others” to the IRB, regulatory agencies, and institutional officials.

For non-VA studies, the ETSU/VA and ETSU IRB require investigators to promptly submit any problem or event that meets the following criteria to the IRB within 10 working days using the Form 109 (unanticipated problem report) signed by the PI.

For VA studies, VA reporting requirements require immediate reporting of the loss or theft of VA research data/information or portable media such as laptops or personal computers- see Section III. VA reporting requirements require Investigators, VA Research Compliance Officers, and other members of the VA research community to report all problems involving, or suggesting, risks to subjects or others in VA Research to the Associate Chief of Staff for Research (ACOS for R) and the ETSU/VA IRB as soon as possible but no later than five business days after becoming aware of the problem.

Events to be reported include:

- a. any event, including on-site and off-site adverse events, injuries, side effects, deaths, or other problems, which in the opinion of the local PI, was unexpected, , suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized , and was related to or possibly related to the research.\*
- b. Any accidental or unintentional change to the IRB-approved protocol that involves risks or has the potential to recur
- c. Any deviation from the protocol taken without IRB approval to eliminate apparent immediate hazard to a research participant
- d. Any publication in the literature, safety monitoring report,(including Data and Safety Monitoring Reports), interim result, or other finding that indicates an unexpected change to the risk/benefit ratio of the research.
- e. Any breach in confidentiality that may involve risk to the participant or others
- f. Any complaint of a participant that indicates an unanticipated risk or that cannot be resolved by the research staff
- g. any local death, whether anticipated or not
- h. incarceration of a participant
- i. Any other possibly related event which in the opinion of the investigator constitutes an unanticipated risk.
- j. Addition of a black box warning on any drug used in your research (for VA studies, this also includes VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to a VA research study
- k. interruptions of subject enrollment or other research activities due to concerns about the safety, rights, or welfare of human research subjects, research staff. or others.
- l. Any work-related injury to personnel involved in human research, or any research-related injury to any other person, requiring more than minor medical intervention or that leads to serious complication or death.
- m. Any Data Monitoring Committee (DMC) report or any sponsor analysis describing a safety problem

- n. For VA studies, any local Serious Adverse Event (see definition)
- o. For VA studies, any problem that involves or suggests risks to VA research subjects or anyone else in VA research.

### **III. Non-VA PI Responsibilities regarding Adverse Event Assessment (category a above) SEE SECTION IV for VA studies**

#### **A. Internal adverse events**

Upon becoming aware of an internal adverse event, PIs are required to promptly assess the event and determine whether the event is a UPIRTSO. PIs must evaluate each event by the following three criteria in order to make that determination.

If the answer to the three following questions is “yes”, then the event is a UPIRTSO and must be submitted to the IRB within 10 working days using the Form 109.

1. Is the adverse event unexpected?
2. Is the adverse event related or possibly related to participation in the research?

Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized? \*

\*Note: If the adverse event is serious (see definition above), the answer to this question is always “yes”.

If the answer to all three questions is “yes” then the event meets the definition of a UPIRTSO and must be reported to the IRB within 10 working days on a form 109 and a modification request. The modification request must outline the necessary revisions to the IRB approved protocol, consent document or other associated documents to incorporate the event’s impact on the risk-potential benefit profile of the study.

If all three questions are not answered “yes”, then the event does not meet the definition of a UPIRTSO. The event is not required to be reported to the IRB within 10 days but is reportable to the IRB in summary format at the time of continuing review.

Regardless of the determination, PIs also are responsible for ensuring that the adverse event is reported to the monitoring entity if required under the monitoring provisions described in the IRB-approved protocol or by institutional policy.

#### **B. External adverse events**

When PIs receive a report of an external adverse event, PIs are required to promptly assess the event and determine whether the event is a UPIRTSO. Only external adverse events that are identified as meeting the three criteria above must be reported promptly to the IRB as UPIRTSOs. If all three questions are not answered “yes”, then the event does not meet the definition of a UPIRTSO. The event is not required to be reported to the IRB within 10 days but is reportable to the IRB in summary format at the time of continuing review. If all three questions are answered

“yes”, then the PI must within 10 days submit BOTH a form 109 and a modification request. The modification request must outline the necessary revisions to the IRB approved protocol, consent document or other associated documents to incorporate the event's impact on the risk-potential benefit profile of the study.

Reports of off-site events occurring in studies that are completed and closed at the local site should be reported if the event meets the IRB definition as detailed above AND the local PI judges that this event may affect risk to participants who have completed the study.

Follow-up reports of an off-site event may be submitted on a tracking log without an accompanying Form 109 if the following are true:

- the initial report of the event was submitted as a UPIRTSO on a Form 109
- the local PI has determined that the follow-up information does not contribute meaningful new information

All problems/events that do not meet these criteria should be reported to the IRB in summary form (table or spreadsheet) at the time of continuing review.

## **IV. VA PI Responsibilities regarding Adverse Event Assessment (category a above)**

### **A. Internal adverse events**

Upon becoming aware of an internal adverse event, PIs are required to promptly assess the event and make 2 determinations.

#### **1. Is the event a local SAE? (see definition in Section I)**

If the event is a local SAE, the PI must report the event to the ACOS for R and the ETSU/VA IRB using form 109 as soon as possible, but no later than 5 business days after the event has become known to the investigator.

2.If the event is not a local SAE, the PI must evaluate each event by the following three criteria in order to determine whether the event is a UPIRTSO.

If the answer to the three following questions is “yes”, then the event is a UPIRTSO and must be submitted to the IRB within 5 business days using the Form 109 and a modification request. The modification request must outline the necessary revisions to the IRB approved protocol, consent document or other associated documents to incorporate the event's impact on the risk-potential benefit profile of the study.

1. Is the adverse event unexpected?
2. Is the adverse event related or possibly related to participation in the research?
3. Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

If all three questions are not answered “yes”, then the event does not meet the definition of a UPIRTSO. The event is not required to be reported to the IRB within 5 days but is reportable to

the IRB in summary format at the time of continuing review. Regardless of the determination, PIs also are responsible for ensuring that the adverse event is reported to the monitoring entity if required under the monitoring provisions described in the IRB-approved protocol or by institutional policy.

## B. External adverse events

When PIs receive a report of an external adverse event, PIs are required to promptly assess the event and determine whether the event is a UPIRTSO. Only external adverse events that are identified as meeting the three criteria above must be reported promptly to the IRB as UPIRTSOs. If all three questions are not answered "yes", then the event does not meet the definition of a UPIRTSO. The event is not required to be reported to the IRB within 5 days but is reportable to the IRB in summary format at the time of continuing review. If all three questions are answered "yes", then the PI must within 5 business days submit BOTH a form 109 and a modification request. The modification request must outline the necessary revisions to the IRB approved protocol, consent document or other associated documents to incorporate the event's impact on the risk-potential benefit profile of the study.

Reports of off-site events occurring in studies that are completed and closed at the local site should be reported if the event meets the IRB definition as detailed above AND the local PI judges that this event may affect risk to participants who have completed the study.

Follow-up reports of an off-site event may be submitted on a tracking log without an accompanying Form 109 if the following are true:

- the initial report of the event was submitted as a UPIRTSO on a Form 109
- the local PI has determined that the follow-up information does not contribute meaningful new information

All problems/events that do not meet these criteria should be reported to the IRB in summary form (table or spreadsheet) at the time of continuing review.

## **V. \*VA Reporting of Loss or Theft of VA research data/information**

The loss or theft of VA research data/information or portable media such as laptops or personal computers must be immediately reported (as soon as it is discovered that there has been a loss) as follows:

Report the loss to security/ police officers IMMEDIATELY. If within, a VA health care facility, notify the VA police. If the loss or theft occurs while on travel or at another institution, notify the security police officers at the institution (such as hotel security, university security, etc.) as well as the police in the jurisdiction where the event occurred.

Obtain the case number and the name and badge number of the investigating officer. If possible, a copy of the case report should be obtained.

Report the incident IMMEDIATELY to

your immediate supervisor\*

VA Privacy Officer at your facility \*

VA Information Security Officer at your facility\*

ACOS at your facility\*

4. Report the incident to the IRB using a Form 109 (Unanticipated Problem Involving Risks to Subjects or Others).

\* The name and contact information should always be readily available. Wallet cards that list the contact name and number of the James H. Quillen VA ACOS, the VAMC Privacy Officer and the VAMC Information Security Officer are available through the VA R&D office and the IRB Office.

## **VI. IRB Responsibilities**

The IRB Coordinator will present the written report of the unanticipated event received from the investigator to the IRB Chair within 5 days.\* (SEE EXCEPTION BELOW FOR VA STUDIES). The Chair will perform an initial review, and determine whether the event is an unanticipated problem involving risks to participants or others. In addition, for VA studies, the Chair will determine and document on the UPIRTSO Reviewer Form whether the problem or local SAE is serious, unanticipated, or related or possibly related. The Chair determines the action required based on his/her decision. If the Chair determines that the event is not a UPIRTSO, no further action is taken. If the Chair determines that the event is a UPIRTSO, the Chair will consider suspension or other immediate action such as notification of participants and refer the report to the IRB. If the Chair determines that there is the potential of immediate harm to participants, the Chair may immediately suspend the study pending the IRB's receipt and review of the unanticipated problem and determination of any required actions.

If Chair determines that the report is a UPIRTSO, the report, with any attached documents, the narrative description of the project, and the current approved informed consent, will be forwarded to the IRB Primary Unanticipated Problem (UP) Reviewer for initial review. The UP Reviewer, appointed by the IRB, will review all UPIRTSOs submitted and report findings and any recommendations for local ICD revisions to the IRB. In addition, all IRB members receive a copy of the Unanticipated Event Form (Form 109), the narrative description of the project, and the currently approved consent document. If additional information is required in order to make a final determination concerning the event, the investigator will receive such a request in writing from the Chair/Board. The report will be added to the next agenda for the convened board. VA events requiring review by the convened board must be reviewed at the IRB's next convened meeting. Refer to Policy 34 for VA reporting requirements.

Examples of corrective actions or substantive changes that might need to be considered by the IRB in response to a UPIRTSO include:

- a. Modification of inclusion or exclusion criteria to mitigate the newly identified risk
- b. Implementation of additional procedures for monitoring subjects
- c. Suspension of enrollment of new subjects
- d. Suspension of research procedures in currently enrolled subjects
- e. Modification of informed consent documents to include a description of newly recognized risks
- f. Provision of additional information about newly recognized risks to previously enrolled subjects (if IRB determines that an informed consent modification is warranted, the convened IRB must determine and document in the minutes whether or not previously enrolled subjects must be notified of the modification and if so, when such modification must take place and how such notification must be documented)
- g. Reconsideration of study approval

- h. Revision of the continuing review timetable
- i. Requirement of notification of past participants

The IRB may deem it necessary to directly audit the research site and medical records pertaining to the event, monitor the consent process, interview participants or witnesses, or suspend/withdraw IRB approval until such time that the safety of the participants can be assured. If information that may relate to subject's willingness to continue to take part in the research is noted, the IRB will require notification of current participants. The IRB may require that current participants be re-consented. The IRB may terminate the research.

Correspondence will be forwarded to the Principal Investigator as per the decision of the IRB following the completion of the review process.

If the Chair determines the event is a UPIRTSO, the reporting requirements outlined in Policy 34 will be followed.

The ETSU/VA IRB Chair is responsible for reviewing any report of a local death to determine if the death is unanticipated. For VA studies, if the Chair determines that the death is unanticipated, the ETSU/VA IRB Coordinator immediately forwards the Chair's written assessment to the VA AO. The VA AO is responsible for submitting the report to ORO within 24 hours of the Chair's determination that the death was unanticipated.

If the local site submits a tracking log for non-reportable events to satisfy sponsor requirements, the events/problems listed on the tracking log will be acknowledged by the IRB Chair, as indicated by his/her initials and date in the final column of the tracking log. A copy of the log will be filed with the study file, and the original returned to the investigator.

\*For VA studies,

If the IRB receives a report of a reported loss or theft of VA research data/information or portable media, the report will be immediately forwarded to the HRPP Director. The HRPP Director will immediately follow the reporting pathway outlined in Section III above.

## References

45 CFR 46. 103(b)(4)(iii)

21 CFR 56.108(b)(1)

OHRP Compliance

45 CFR 46 104(a)

45 CFR 35 104 (b)

VHA Handbook 1058.1

Appendix A, Memo from Deputy Under Secretary for Health Operations and Management (DUSHOM) and Chief Research and Development Officer (CRADO) dated February 6, 2007

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events dated January 15, 2007

VHA Handbook 1058.01 February 27, 2009

## **IRB STAFF**

***Janine Richardson, OPHRS Director***

423- 4939-6054  
richardf@etsu.edu

***Teresa Doty, IRB Coordinator (Medical)***

423- 439-6055  
doty@etsu.edu

***TBD, IRB Coordinator (Campus)***

423- 439-6002

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## **VA Administration Staff**

***Owen Murnane, Ph.D.***

***Associate Chief of Staff for Research***

423-979-2859  
Owen.murnane@med.va.gov

***Paul Williamson***

***Research Administrative Officer***

423-979-2662  
Paul.williamson@med.va.gov

***Sharon Neas***

***Research Administrative Assistant***

423-979-2859  
Sharon.neas@va.gov