January 17, 2019

TEMPORARY ADDENDUM TO ALL DURHAM VA HEALTH CARE SYSTEM HUMAN RESEARCH PROTECTIONS PROGRAM STANDARD OPERATING PROCEDURES, version July 2018.

PURPOSE: This Standard Operating Procedure (SOP) is an addendum to the *Policies and Standard Operating Procedures for the Durham Veterans Affairs Health Care System Human Research Protection Program* (Durham VAHCS HRPP SOP) and describes the variations in requirements and procedures that the Durham VA Health Care System (DVAHCS) HRPP, Institutional Review Board (IRB), and investigators, will adhere to for research subject to the revised Common Rule (2018 Requirements), or determined exempt, on or after January 21, 2019. This SOP also applies to any studies subject to the pre-2018 version of the Common Rule that the DVAHCS decides to transition to comply with the 2018 Requirements.

This addendum to the DVAHCS HRPP SOP also describes the variations in requirements and procedures that the DVAHCS HRPP, IRB, and investigators, will adhere to under VHA Directive 1200.05, dated January 7, 2019. The requirements of appended VHA Directive 1200.05 and the policies and procedures described in this addendum will supersede all rescinded VHA Handbook 1200.05 policies and standard operating procedures described in the DVAHCS HRPP SOP version date July 2018.

When the research invokes multiple regulatory frameworks (e.g., Common Rule, FDA, HIPAA, VHA), all will be applied following this addendum, appended VHA Directive 1200.05, and the procedures described in the DVHACS HRPP SOP that have not been superseded or rescinded by this addendum or VHA Directive 1200.05.

This SOP Addendum will remain in effect until the Durham VAHCS HRPP SOP has been fully updated to incorporate the 2018 Requirements and VHA Directive 1200.05 or if this addendum requires additional interim updates.

1. **2018 Requirements and VHA Directive 1200.05**:
   All human subjects research studies approved by the DVAHCS IRB, or determined exempt, on or after January 21, 2019 will follow the 2018 Requirements under 45 CFR 46 (VA encoded 38 CFR 16).

   Effective January 21, 2019, all human subjects research activities conducted within the Durham VAHCS will follow VHA Directive, *Requirements for the Protection of Human Subjects Research*, dated January 7, 2019.

2. **2018 Requirements Transition Provision**:
   Human subjects research protocols under the pre-2018 Requirements will comply with the pre-2018 Requirements. Studies initially approved by IRB prior to January 21, 2019 may transition to the 2018 Requirements on or after January 21, 2019, and will comply with the 2018 Requirements. Studies will be transitioned on a per-protocol basis.

   The DVAHCS IRB, IRB Chairperson(s), or IRB voting member designated by the IRB Chairperson(s) will determine and document if a study is transitioned to the 2018 Requirements. Requests to transition to the 2018 Requirements must be submitted to IRB and may be done so at the time of continuing review or as an amendment request. Transition requests will include the *Project Transition Checklist* and all protocol documents requiring revision to be compliant with the 2018 Requirements. The date of IRB determination and documentation that the study is approved to transition to the 2018 Requirements is the transition date.

   The IRB will not re-review IRB actions or research-related activities that occurred prior to the transition date to ascertain whether those actions or activities meet the 2018 Requirements. The 2018 Requirements apply only to future actions or activities (i.e., prospectively) beginning on or after the transition date.

   Once a study initiated prior to January 21, 2019 is transitioned to the 2018 Requirements, the decision cannot be reversed, and the study cannot be transitioned back to the pre-2018 Requirements

   For studies subject to the pre-2018 Requirements, provisions of the 2018 Requirements that do not conflict with the pre-2018 Requirements may be implemented. Applying provisions of the 2018 Requirements to research subject to the pre-2018 Requirements does not constitute transitioning a study. For example, studies under the pre-2018 Requirements may implement the new elements of informed consent (2018 Requirements at §46.116(b)(9), (c)(7)-(9)). Without transitioning a study, it is permissible to incorporate these new elements of consent because the pre-2018 Requirements do not prohibit including such information in an informed consent document.

   Studies determined to meet exempt human subjects research status by IRB prior to January 21, 2019 will not be transitioned to the 2018 Requirements.

   FDA regulated studies may not transition to the 2018 Requirements but may implement provisions of the 2018 requirements that are not inconsistent with 21 CFR 50 and 56.

3. **Exempt Categories**:
   Exempt categories 7 and 8 under the 2018 Requirements will not be implemented within the Durham VAHCS.

   Exempt categories 1, 2, 3, 4, 5, and 6 of the 2018 Requirements and as defined in appended VHA Directive 1200.05, will be implemented at the DVAHCS under the regulatory parameters described in both policy documents.

4. **Exempt Determinations and Limited IRB Review**:
   Determinations regarding whether research subject to the 2018 Requirements qualifies for exempt status will be made using expedited review procedures and documented by the IRB Chairperson(s) or IRB voting member designated by the IRB Chairperson(s).

   When the research requires limited IRB review the DVAHCS IRB will document privacy and confidentially provisions (§___.111(a)(7)) are met. When the exempt research requires a HIPAA determination (i.e., HIPAA authorization or waiver of HIPAA authorization), IRB will ensure the HIPAA requirements (45 CFR parts 160 and 164) are met and the appropriate authority approves the HIPAA documents. IRB will approve waivers of HIPAA authorization. As with all other research subject to IRB review requirements, when conducting limited IRB review the IRB has the authority to approve, require modifications in (to secure approval), or disapprove all research activities. [§__.109(a)].

   All exempt research submissions on or after January 21, 2019 must receive ISSO and PO review and approval prior to approval by the Research and Development Committee. If the exempt research requires a HIPAA Authorization, the facility Privacy Officer is responsible for reviewing the HIPAA authorization to ensure legal authority exists prior to the use, access, collection, creation, and disclosure of PHI (obtained orally or in writing) by research investigators.

   All research determined to be exempt requires approval by R&D Committee prior to initiating.

   If exempt research activities involve the investigator interacting or intervening with participants, the following information will be given to prospective participants in writing or orally:
   1. The activity is research;
   2. Participation is voluntary;
   3. Permission to participate can be withdrawn;
   4. Permission for use of data can be withdrawn for exempt research activities involving the collection and use of identifiable data; and
   5. Contact information for the investigator

   If the investigator is requesting exempt category 3 (benign behavioral interventions) under the 2018 Requirements and the intervention involves deception, the verbal or written prospective

agreement must also inform the prospective participant that he/she will be unaware of or misled about the nature or purpose of the research.

The written document or verbal script containing the above elements of prospective agreement will be included in the exempt research application submission to IRB.

5. **Continuing Review**:
For research subject to the 2018 Requirements, unless the IRB determines and documents otherwise, continuing review by IRB is not required in the following circumstances:

    a. Research eligible for expedited review; or
    b. Research reviewed by the IRB in accordance with the limited IRB review; or
    c. Research that has progressed to the point that it involves one or both of the following:
        i. Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
        ii. Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

When the IRB determines that continuing review is required for such research, the rationale will be documented in the IRB minutes and this requirement will be communicated to the investigator in the IRB determination letter.

Non-exempt human subjects research studies under the purview of IRB will not undergo continuing review by R&D Committee.

Research determined to be exempt under the 2018 Requirements, including studies requiring a limited IRB review, require continuing review by the R&D Committee, unless under the oversight of SRS.

FDA regulated studies will continue with requirements under 21 CFR 50 and 56, including a continuing review appropriate for the degree of risk, but no less than once per year.

6. **Broad Consent**:
The Durham VAHCS is not adopting the option for board consent.

7. **Informed Consent**:
When reviewing research subject to the 2018 Requirements the Durham VAHCS IRB will evaluate the provisions for informed consent as described in the HRPP SOP with the below variations. Investigators conducting research subject to the 2018 Requirements must adhere to these requirements. Research under the pre-2018 Requirements and FDA regulated research may implement the informed consent provisions under the 2018 Requirements:

General Requirements for Informed Consent:
The prospective subject or the LAR must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.

Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or LAR in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.

Generally, the beginning of an informed consent should include a concise explanation of the following:

1. The fact that consent is being sought for research and that participation is voluntary;
2. The purpose(s) of the research, the expected duration of the prospective subject's participation, and the procedures to be followed in the research;
3. The reasonably foreseeable risks or discomforts to the prospective subject;
4. The benefits to the prospective subject or to others that may reasonably be expected from the research;

Basic Elements:
One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

a. A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or

b. A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

Additional Elements (must be included when appropriate):
1. A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
2. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions;
3. For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

VA requirements of informed consent:
The following statement will be included in the Durham VAHCS informed consent for all VA research:

> The VA will provide necessary medical treatment should you be injured by being in this study. You will be treated for the injury at no cost to you. This care may be provided by the Durham VAHCS or arrangements may be made for contracted care at another facility. Every reasonable safety measure will be taken to protect your well-being. You have not released this institution from liability for negligence. In case of research related injury resulting from this study, you should contact your study team. If you have questions about compensation and medical treatment for any study related injuries, you can call the medical administration service at this VA Medical Center at 919-286-6957.

The following statement will be included, where appropriate:

> Some Veterans are required to pay co-payments for medical care and services provided by VA. These co-payments requirements will continue to apply to medical care and services provided by VA that are not part of this study.

8. **Posting of Clinical Trial Informed Consent Forms**:
For studies subject to the 2018 Requirements, if a VA research study is a clinical trial, one IRB-approved informed consent form used to enroll subjects, unless the IRB waived documentation of informed consent, must be posted after the clinical trial is closed to recruitment and no later than 60 days after the last study visit by any subject as described in the IRB-approved protocol. The posted informed consent form should be an unfilled version (i.e., no research subject information of any kind) of the approved consent form. For multi-site studies, it applies when the entire study has closed to subject recruitment.

Consent forms must be posted on either https://clinicaltrials.gov or a docket folder on http://Regulations.gov (Docket ID: HHS-OPHS-2018-0021).

For any ORD-funded clinical trial, the applicable ORD funding service will be responsible for posting the informed consent form.

For a clinical trial funded or supported by a Federal agency or department other than VA, the awardee is responsible for posting the informed consent form.

For a clinical trial funded or supported by a non-Federal agency or department (e.g., university, industry, nonprofit organization) or not funded, the VA Investigator conducting the clinical trial is responsible for ensuring that the informed consent form is posted.

If the clinical trial includes multiple sites engaged in the clinical trial, an agreement must exist specifying who is responsible for posting the informed consent form.

If a DVAHCS investigator or employee or agent of the DVAHCS is responsible for posting, the DVAHCS investigator, employee or agent must ensure that the version posted is an unfilled or "blank" template (i.e., do not use a version that has proprietary or personal information such as names and phone numbers) nor attempt to post a redacted version that has been completed by a research subject..

The DVAHCS HRPP is not responsible for ensuring the informed consent form is posted in compliance with VHA Directive 1200.05 if the individual responsible for posting the informed consent is not a Durham VAHCS investigator, employee or agent of the Durham VAHCS.

If a DVAHCS investigator, employee, or agent is responsible for posting the informed consent form, assurance that all posting requirements have been met must be provided to DVAHCS IRB by the time of request for study closure.

9. **Waiver or Alteration of Informed Consent**:
When reviewing research subject to the 2018 Requirements, in addition to the criteria described in the DVAHCS HRPP SOP, the IRB may also approve a request for a waiver or alteration of informed consent if it finds that:

If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;

The IRB's determination will be documented in the IRB record and communicated to the investigator as described in the HRPP SOP.

10. **Screening, Recruiting, or Determining Eligibility**:
Pursuant to the 2018 Requirements, the DVAHCS IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purposes of screening, recruiting, and determining eligibility without the informed consent of the prospective subject or the subject's LAR if either of the following conditions is met:

    1. The investigator will obtain information through oral or written communication with the prospective subject or LAR, or
    2. The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

When prospective studies involving interventions or interactions with participants are subject to the 2018 Requirements, investigators do not have to request waivers of consent for the purposes of screening, recruiting, or determining eligibility but the above conditions must be described in the DVAHCS protocol submitted to the IRB.

A waiver of HIPAA authorization must be approved by IRB prior to accessing any PHI for screening, recruiting, and determining eligibility.

11. **Waiver of Documentation of Informed Consent:**
When reviewing research subject to the 2018 Requirements, in addition to the criteria described in the DVAHCS HRPP SOP, the IRB may also approve a request for a waiver of documentation of consent if it finds that:

1. The subjects or LARs are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects, and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

The IRB's determination will be documented in the IRB record and communicated to the investigator, as described in the DVAHCS HRPP SOP.

12. **IRB Review of Grant Applications:**
The Durham VAHCS IRB is not required to review Federal grant applications for new research proposals submitted to IRB on or after January 21, 2019. Grant applications may be reviewed by the IRB if requested by IRB or if request or required by the Federal department or agency conducting or supporting the research.

13. **HIPAA Authorization:**
The HIPAA authorization may be combined with the research informed consent, attached to the informed consent form, or a standalone document. If the HIPAA Authorization is a standalone document or attached to the informed consent form, VA Form 10-0493, *Authorization to Use and Release of Individually Identifiable Health Information Collected for VHA Research*, will be used. If VA Form 10-0493 is used, the DVAHCS Privacy Officer (PO) will annotate on the form the date of review and approval.

If the HIPAA authorization is combined with the research consent, all elements required by the HIPAA Privacy Rule and VHA Directive 1605.01 will be incorporated into the research consent document. The IRB will approve the informed consent document that incorporates all elements of HIPAA authorization. The date of IRB approval will be documented on the first page of the informed consent document. The DVAHCS PO will review the HIPAA authorization section of the informed consent to ensure it contains all required elements and is consistent with all privacy requirements.

14. **Multisite Research and Single IRB Provision:**
For multi-site protocols an IRB from a non-affiliated medical or dental school may be used if that IRB has been specifically designated by ORD as an IRB that may serve as a multi-site IRB for VA facilities.

When the DVAHCS engages the services of another entity's IRB as its IRB of record, the IO is responsible for establishing and signing a Memorandum of Understanding (MOU) or Authorizing Agreement with external organizations providing IRB services and ensuring

external IRBs or record used by the DVAHCS hold current IRB registrations with FDA/OHRP and provide membership updates as required by VHA Handbook 1058.03.

The DVAHCS IRB cannot serve as the IRB of record for any non-VA entity except for a Department of Defense (DoD) facility, Department of Energy laboratory, or the NPC.

JOHN D. WHITED 399178 Digitally signed by JOHN D. WHITED 399178 Date: 2019.01.17 14:31:29 -05'00'

John Whited, M.D.
Associate Chief of Staff, Research and Development

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David Edelman, M.D.
Durham VAHCS IRB Chair

APPENDIX A

VHA Directive 1200.05, *Requirements for the Protections of Human Subjects in Research,* dated January 7, 2019. https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=8171

POLICIES AND STANDARD OPERATING PROCEDURES FOR THE DURHAM VETERANS AFFAIRS HEALTH CARE SYSTEM HUMAN RESEARCH PROTECTION PROGRAM

VA Mid-Atlantic Health Care Network

VAMC DURHAM

A PUBLICATION OF THE RESEARCH AND DEVELOPMENT SERVICE
DURHAM VAHCS
508 Fulton Street
Durham, North Carolina 27705

July 2005
Revised: October 2006, April 2008, September 2008, September 2009, October 2010, March 2011, May 2011, November 2011, January 2013, March 2013, August 2013, and June 2014, March 2015, August 2015, December 2015, April 2016, October 2016, May 2017

CURRENT: July 2018

REVISIONS

Revisions from October 2017 to July 2018 include:

SOP #	Title	Change
SC 504	**1.3 VA Central Institutional Review Board (CIRB) Studies**	Revised the process for local review of studies under the purview of VA CIRB. Primary change involves R&D no longer reviewing individual amendments, modifications, or updates approved by CIRB.

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Mission Statement

MISSION STATEMENT

The overarching mission of the Human Research Protection Program (HRPP) at the Durham VAHCSis to protect the rights and welfare of human research participants recruited to participate in research conducted under the auspices of the Durham VAHCS. Rather than ensuring mere compliance with the federal regulations, the Durham VA HRPP strives to adhere to the highest ethical standards in its protection of human research participants and seeks to further develop the methods and mechanisms for protecting human research participants. In service of this mission, the HRPP endeavors to:

- Create an atmosphere of respect for, and awareness of, the rights and welfare of human research participants at the Durham VAHCS.
- Continue to inform established researchers about the application of the federal regulations and ethical principles to their particular area of research in an effort to keep researchers current with evolving standards.
- Educate students, faculty, and staff who conduct research about the ethical principles and federal regulations guiding research with humans.
- Assess the effectiveness of the Institutional Review Board (IRB) in its review of research activities, facilitation of compliance of researchers with the federal regulations, and protection of research participants.
- Develop new approaches that better serve the overarching mission of the HRPP, such as state-of-the-art educational materials, more efficient methods for processing applications, tracking and monitoring research activities, and assessing the overall effectiveness of the HRPP.

Introduction

INTRODUCTION

Regulations require that Institutional Review Boards (IRBs) have written policies and procedures, and that activities at the institution are carried out as described in the written policies and procedures document. These Standard Operating Policies and Procedures (SOP) are written to enable the Durham VAHCS IRB to maintain a system of compliance. The SOPs of an IRB reflect not only the laws and regulations, but also the underlying ethical principles that are the basis of the IRB's mandate. Finally, these policies also reflect the overarching commitment of the Durham VAHCS's Human Research Protections Program (HRPP) to provide protection for all human subjects involved in research conducted under the direction of its students, staff and faculty.

The ethically responsible researcher is expected to carry the dual burden to advance knowledge that can improve the human condition or generate new knowledge and, at the same time, to recognize the absolute imperative to treat human research subjects with the utmost care and respect.

It is not unreasonable to ask others to share this burden, indeed, the institutions, sponsors, and society as a whole who expect to benefit from this research should be expected to share in the responsibility of conducting ethical research.

This burden also falls, then, to the men and women who sit on Institutional Review Boards. They are, certainly, expected to act as gatekeepers, to apply proper oversight of the research enterprise in its drive to find the newest therapy and to advance knowledge of the basics of biological and behavioral mechanisms, and they are expected to share the responsibility of protecting the human subjects of this research.

These SOPs apply to all the day-to-day operations of the IRB. The SOPs apply to all members of the IRB, all members who serve on it as part of their overall institutional responsibilities, and all others who must subscribe to its decisions and its requirements (for example, the clinical Investigators, research managers/coordinators, research nurses, support staff, etc.). Inspection of a Human Research Protections Program (HRPP) by the FDA, the accrediting organization under contract with VA , Office for Human Research Protections (OHRP) and the Office for Research Oversight (ORO) inspection of an IRB always includes an assessment of the IRB's SOP.

These SOPs will be reviewed every two years or as necessary to ensure that they are up-to-date, that new legislation or regulations are reflected in the policies and that daily activities are being performed as described in the SOPs.

These policies are based on current regulations, ethical principles, and guidelines for the protection of the human subjects of biomedical and behavioral research. As guidelines and regulations change in response to new technologies, new interpretation of principles, and other emerging issues, it is recognized that policies and procedures are evolving through the practice of human research protection. These evolving policies and procedures may require an implementation period for assessment prior to

standardizing them in the SOP. The policies state what the Durham VAHCS's HRPP requires for the ethical conduct of clinical research. The procedures detail how these policies are carried out.

The policies and procedures are not an end unto themselves. They are the framework upon which research activities in the Durham VAHCS are conducted. Therefore, all members of the research enterprise who are working within this institution are expected to read, understand, and comply with them. This way, the burden of conducting sound, effective and ethical research can be shared.

Abbreviations

ABBREVIATIONS

ACOS/R&D	Associate Chief of Staff for Research & Development
ADE	Adverse Drug Event/Experience
AE	Adverse Event
AO/R	Administrative Officer for Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practice
CIOMS	Council for International Organizations of Medical Science
CLIA	Clinical Laboratory Improvement Act
CPRS	Computerized Patient Record System
CRA	Clinical Research Associate
CRADO	Chief Research and Development Officer
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRO	Contract Research Organizations
CSP	Cooperative Studies Program (VA)
CSPCC	Cooperative Studies Program Coordinating Center (VA)
CRPCC	Clinical Research Pharmacy Coordinating Center (VA)
DHHS	Department of Health and Human Services (or HHS)
DoD	Department of Defense
DPAHC	Durable Power of Attorney for Health Care
DSMB	Data Safety and Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HRPP	Human Research Protections Program
IBC	Institutional Biosafety Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IDMC	Independent Data Monitoring Committee
IMR	Institute for Medical Research
IEC	Independent Ethics Committee
IND	Investigational New Drug
IO	Institutional Official
IRB	Institutional Review Board
IVD	In Vitro Diagnostic
LAR	Legally Authorized Representative
MCD	Medical Center Director
NDA	New Drug Application
NIH	National Institutes of Health

Abbreviations

OHRP	Office for Human Research Protections (former OPRR)
OPRR	Office for Protection from Research Risks
ORD	Office of Research and Development
ORO	Office of Research Oversight
PI	Principal Investigator
PHS	Public Health Service
PMA	Premarket Approval (Application)
QA	Quality Assurance
QC	Quality Control
RAC	Recombinant DNA Advisory Committee (NIH)
SAE	Serious Adverse Event
SMART	Site Monitoring and Review Team (VA)
SOP	Standard Operating Procedure
UAE	Unexpected Adverse Event
WOC	Without Compensation

Lay Language for Informed Consent

LAY LANGUAGE FOR INFORMED CONSENT

Term	Definition
acute	new, recent, sudden
adverse effect	side effect
assay	lab test
benign	not malignant, usually without serious consequences
bolus	an amount given all at once
carcinogenic	capable of causing cancer
catheter	a tube for withdrawing or introducing fluids
chronic	continuing for a long time
clinical trial	an experiment with patients
controlled trial	a study in which the experimental procedures are compared to standard (accepted treatments or procedures
culture	test for infection, or organisms that could cause infection
double blind	study in which neither the Investigators nor the subjects know which intervention the subject is receiving
dysplasia	abnormal cells
edema	increased fluid
efficacy	effectiveness
extravasate	to leak outside of a blood vessel
hematoma	a bruise, a black and blue mark
heparin lock	needle placed in the arm with blood thinner to keep the blood from clotting
monitor	check on, keep track of, watch carefully
morbidity	undesired result or complication
mortality	death or death rate
necrosis	death of tissue
oncology	the study of tumors or cancer
percutaneous	through the skin
placebo	a substance of no medical values, an inactive substance
PRN	as needed
protocol	plan of study
random	by chance, like the flip of a coin
relapse	the return of a disease
retrospective	looking back over past experience

Glossary

GLOSSARY

510(K) DEVICE	A medical device that is considered substantially equivalent to a device that was or is being legally marketed. A Sponsor planning to market such a device must submit notification to the FDA 90 days in advance of placing the device on the market. If the FDA concurs with the Sponsor, the device may then be marketed. 510(k) is the section of the Food, Drug and Cosmetic Act that describes premarket notification; hence the designation "510(k) device."
ADVERSE EVENT	An AE is any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigation test article. An AE does not necessarily have to have a causal relationship with the research.
ADVERSE EVENT REPORT	Report to appropriate institutional officials about adverse events.
ADVERTISING	One mechanism or method used by researchers to recruit subjects for research studies.
AGENT	An agent of the Durham VAHCS includes employees who are 1) compensated by the VA and have a VA appointment; 2) appointed to work without compensation (WOC); or 3) assigned to VA through the Intergovernmental Personnel Act (IPA). Contractors are not considered agents of the VA.
ALTERNATIVES	Options that exist for a subject who is thinking about participating in research.
ANONYMITY	The condition that exists when there are no identifiers on research materials that could link or identify the data to an individual subject even to the research Investigators.
ARENA	Applied Research Ethics National Association: a membership organization for individuals interested in ethical issues relating to medicine and research.
ASSENT	Agreement by an individual not competent to give legally valid informed consent (*e.g.*, a child or cognitively impaired person) to participate in research.
ASSURANCE	An Assurance is a written commitment by an institution to protect human subjects participating in research. Under federal regulations, any institution conducting or engaged in federally

	supported research involving human subjects must obtain an Assurance in accordance with 38 CFR 16.103. ***NOTE****: All research conducted under VA auspices is considered to be Federally-supported.* This requirement also applies to any collaborating "performance site" institutions. Also called an Assurance of Compliance, or a Federal-wide Assurance (FWA).
AUTHORIZED INSTITUTIONAL OFFICIAL	An individual at an institution with the authority to speak for, and legally commit the institution to adherence to the requirements of the federal regulations regarding the involvement of human subjects in biomedical and behavioral research and ensure effective administration and implementation of the institution's system for the protection of human subjects.
AUTONOMY	Personal capacity to consider alternatives, make choices, and act without undue influence or interference of others.
BANKED SPECIMEN	Human biological specimens and linked clinical data collected as part of a research project and stored in a VA-approved bank for future use.
BELMONT REPORT	A statement of basic ethical principles governing research involving human subjects issued by the National Commission for the Protection of Human Subjects in 1978.
BENEFICENCE	An ethical principle discussed in the Belmont Report that entails an obligation to protect persons from harm. The principle of beneficence can be expressed in two general rules: (1) do not harm; and (2) protect from harm by maximizing possible benefits and minimizing possible risks of harm.
BENEFIT	A valued or desired outcome; an advantage.
BIOLOGIC	Any therapeutic serum, toxin, anti-toxin, or analogous microbial product applicable to the prevention, treatment, or cure of diseases or injuries.
BLIND STUDY DESIGNS	A study design comparing two or more interventions in which the Investigators, the subjects, or some combination thereof, do not know the treatment group assignments of individual subjects; it is sometimes called a masked study design.
CASE HISTORY	A case history is a record of all observations and other data

	pertinent to the investigation on each research subject. An Investigator is required to prepare and maintain adequate and accurate case histories. 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. (See definition of Research Record).
CASE-CONTROL STUDY	A study comparing persons with a given condition or disease (the cases) and persons without the condition or disease (the controls) with respect to antecedent factors. (*See also: Retrospective Studies*.)
CDC	Centers for Disease Control and Prevention; an agency within the Public Health Service, Department of Health and Human Services.
CERTIFICATE OF CONFIDENTIALITY	A Certificate of Confidentiality protects the compelled release of identifiable information about research subjects in any legal proceeding. These documents are issued by the DHHS and can be requested for all research, regardless of funding source [42 USC 241(d)]. VA does not issue its own Certificates of Confidentiality.
CERTIFICATION	The human subject regulations, in certain parts require the Institutional Review Board (IRB) to provide a "certification" to the government. For example, see the prisoner regulations at 45 CFR Part 46, Subpart C.
CHAIRPERSON / CO-CHAIRPERSON	The person who leads the activities of the IRB.
CHILDREN	Persons who have not attained the legal age for consent to treatment or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted.
CLASS I, II, III DEVICES	Classification by the Food and Drug Administration of medical devices according to potential risks or hazards.
CLINICAL INVESTIGATION	Any experiment that involves a test article and one or more human subjects that is subject to Food and Drug Administration (FDA) requirements for research or marketing permits [21 CFR Part 50.3 (c) and 56.102 (c)].

Glossary

CLINICAL TRIAL	A controlled study involving human subjects, designed to contribute to generalizable knowledge and to evaluate prospectively the safety and effectiveness of new drugs or devices or of behavioral interventions.
COERCION	The act of inducing or pressuring an individual to consent to participate in research or to stay in research.
CODE OF FEDERAL REGULATIONS (CFR)	The federal compendium of regulations on numerous topics related to compliance with federal laws.
CODED DATA	The term “coded data” means “coded private information” as defined in guidance published by HHS entitled Guidance on Research Involving Coded Private Information or Biological Specimens, currently available at: http://www.dhhs.gov/ohrp/humansubjects/guidance/cdebiol.htm (see VHA Handbook 1200.12). In general, “coded” means that (1) identifying information including all 18 HIPAA identifiers listed in 45 CFR 164.514 has been replaced with a number, letter, symbol, or combination thereof (i.e., the code) and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.
COGNITIVELY IMPAIRED	Having either a psychiatric disorder (*e.g.*, psychosis, neurosis, personality or behavior disorders, or dementia) or a developmental disorder (*e.g.*, mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.
COHORT	A group of subjects initially identified as having one or more characteristics in common who are followed over time. In social science research, this term may refer to any group of persons who are born at about the same time and share common historical or cultural experiences.
COMMON RULE	Title 45 CFR 46 Subpart A ("The Common Rule") is the basic set of protections for all human subjects research conducted or supported by the US Dept. of Health & Human

	Services.
COMPENSATION	Payment or other benefits that will be given to subjects who volunteer to participate in research protocols. (*Compare: Remuneration*.)
COMPETENCE	Technically, a legal term, used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. (*See also: Incompetence, Incapacity*.)
CONFIDENTIALITY	Pertains to privacy and non-disclosure of personal information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure.
CONFLICT OF INTEREST	A financial or perceived conflict of interest occurs when any financial arrangement, situation or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results or reporting of research activities or findings.
CONSENT	Agreement to do something. Informed consent is agreement to do something based upon a complete understanding of that task.
CONTRACT	An agreement that a specific research activity will be performed at the request, and under the direction of, the agency providing the funds. Research performed under contract is more closely controlled by the agency than research performed under a grant. (*Compare: Grant*.)
CONTRA-INDICATED	Pertains to the use of a treatment that should not be used in certain individuals or conditions due to risks of disadvantageous, perhaps dangerous results (*e.g.*, a drug may be contraindicated for pregnant women and persons with high blood pressure).
CONTROL (SUBJECTS) OR CONTROLS	Subject(s) used for comparison who are not given a treatment under study or who do not have a given condition, background, or risk factor that is the object of study. Control conditions may be concurrent (occurring more or less simultaneously with the condition under study) or historical (preceding the condition under study). When the present condition of subjects is compared with their own condition on a prior regimen or treatment, the study is considered historically controlled.

Glossary

CONTINUING REVIEW	The regulatory requirement that the Institutional Review Board (IRB) review research at intervals not greater than one year. The IRB may review research at more frequent intervals [45 CFR 46.109(e); 21 CFR 56.109(f)].
CROSS-OVER DESIGN	A type of clinical trial in which each subject experiences, at different times, both the experimental and control therapy. For example, half of the subjects might be randomly assigned first to the control group and then to the experimental intervention, while the other half would have the sequence reversed.
DATA	Data means information derived directly from patients or human subjects or indirectly through accessing databases. It includes information from DNA sequencing.
DATABASE	A collection of data or information elements organized in a manner to permit systematic retrieval.
DATA MONITORING COMMITTEE (DMC), DATA AND SAFETY MONITORING BOARD (DSMB), OR DATA AND SAFETY MONITORING COMMITTEE (DSMC)	A DMC, DSMB, or DSMC is a group of individuals with relevant expertise that reviews accumulating data from one or more ongoing research studies. The DMC, DSMB, or DSMC independently advises the sponsor or the PI regarding the continuing safety of the research study's subjects, as well as the continuing validity and scientific merit of the study.
DATA REPOSITORY	A database or a collection of databases that have been created or organized to facilitate the conduct of multiple research protocols, including future protocols not yet envisioned. It also may have been created for other purposes such as administrative and clinical purposes.
DEBRIEFING	Giving subjects previously undisclosed information about the research project following completion of their participation in research. (Note that this usage, which occurs within the behavioral sciences, departs from standard English, in which debriefing is obtaining rather than imparting information.)
DECEPTION STUDY	A research study that incorporates in the design a technique for intentionally misleading a human subject during the course of the study to obtain certain results. The subject is

	debriefed after the study ends or after their participation ends.
DECLARATION OF HELSINKI	A code of ethics for clinical research approved by the World Medical Association in 1964 and widely adopted by medical associations in various countries.
DE-IDENTIFIED DATA	For the purposes of VA research, de-identified data are data that have been de-identified in accordance with both: (a) The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (45 CFR 164.514(b) and (b) The Common Rule provision that the identity of the subject cannot be readily ascertained by the Investigator or be associated with the information (38 CFR 16.102(f)). Such data may also be known as "anonymous". ***NOTE:*** *Coded data is data identifiable by the individual(s) who has access to the code. Therefore, coded data are <u>not</u> considered to be de-identified or anonymous.*
DEPENDENT VARIABLES	The outcomes that are measured in an experiment. Dependent variables are expected to change as a result of an experimental manipulation of the independent variable(s).
DESCRIPTIVE STUDY	Any study that is not truly experimental (*e.g.*, quasi-experimental studies, correlational studies, record reviews, case histories, and observational studies).
DEVICE (MEDICAL)	See: Medical Device.
DIAGNOSTIC (PROCEDURE)	Tests used to identify a disorder or disease in a living person.
DOUBLE-MASKED DESIGN	A study design in which neither the Investigators nor the subjects know the treatment group assignments of individual subjects. Sometimes referred to as "double-blind."
DRUG	Any chemical compound that may be used on or administered to humans as an aid in the diagnosis, treatment, cure, mitigation, or prevention of disease or other abnormal conditions.
EMANCIPATED MINOR	A legal status conferred upon persons who have not yet attained the age of legal competency law (for such purposes as consenting to medical care), but who are entitled to treatment as if they had by virtue of assuming adult responsibilities such as being self-supporting and not living at home, marriage, or procreation.

Glossary

EMBRYO	Early stages of a developing organism, broadly used to refer to stages immediately following fertilization of an egg through implantation and very early pregnancy (*i.e.*, in humans, from conception to the sixth week of pregnancy).
EMERGENCY USE	Use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval.
EPIDEMIOLOGY	A scientific discipline that studies the factors determining the causes, frequency, and distribution of diseases in a community or given population.
EQUITABLE	Fair or just; used in the context of selection of subjects to indicate that the benefits and burdens of research are fairly distributed.
ETHICS ADVISORY BOARD	An interdisciplinary group that advises the Secretary, HHS, on general policy matters and on research proposals (or classes of proposals) that pose ethical problems.
ETHNOGRAPHIC RESEARCH	Ethnography is the study of people and their culture. Ethnographic research, also called fieldwork, involves observation of and interaction with the persons or group being studied in the group's own environment, often for long periods of time. (*See also: Fieldwork*.)
EXCULPATORY	Pertaining to that which relieves of a responsibility, obligation, or hardship; clearing from accusation or blame.
EXEMPT RESEARCH	Research activities determined by the Institutional Review Board (IRB) to involve human subjects only in one or more of certain categories (38 CFR 16.101(b)).
EXPANDED AVAILABILITY	Policy and procedure that permits individuals who have serious or life-threatening diseases for which there are no alternative therapies to have access to investigational drugs and devices that may be beneficial to them. Examples of expanded availability mechanisms include Treatment INDs, Parallel Track, and open study protocols.
EXPEDITED REVIEW	In contrast to a convened IRB review process, the expedited review process consists of a review carried out by the IRB Chair or by one or more experienced voting members of the IRB designated by the IRB Chair in accordance with 38 CFR 16.110(b).

Glossary

EXPERIMENT	Generally, this refers to an intervention or interaction that is unproven and not yet scientifically validated.
EXPERIMENTAL	Term often used to denote a therapy (drug, device, procedure) that is unproven or not yet scientifically validated with respect to safety and efficacy. A procedure may be considered "experimental" without necessarily being part of a formal study (research) to evaluate its usefulness. (*See also: Research*.)
EXPERIMENTAL SUBJECT	For Department of Defense (DoD) research, research involving a human being as an “experimental subject” is an activity, for research purposes, where there is an intervention or interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction [32 CFR 219.102(f), reference (c)]. Examples of interventions or interactions include, but are not limited to, a physical procedure, a drug, a manipulation of the subject or subject’s environment, the withholding of an intervention that would have been undertaken if not for the research purpose. This does not include: • Activities carried out for purposes of diagnosis, treatment, or prevention of injury and disease in members of the Armed Forces and other mission essential personnel under Force Health Protection programs of the Department of Defense. • Authorized health and medical activities as part of the reasonable practice of medicine or other health professions. • Monitoring for compliance of individuals and organizations with requirements applicable to military, civilian, or contractor personnel or to organizational units. This includes such activities as drug testing, occupational health and safety monitoring, and security clearance reviews. • Activities exempt under 32 CFR Part 219 (reference (c)).
EXPERIMENTAL STUDY	A true experimental study is one in which subjects are randomly assigned to groups that experience carefully controlled interventions manipulated by the experimenter according to a strict logic allowing causal inference about the effects of the interventions under investigation. (*See also: Quasi-Experimental Study*).
FAMILY MEMBER	One who is part of the basic unit in society traditionally consisting of two parents rearing their own or adopted children; *also***:** any of various social units differing from but regarded as equivalent to the traditional family.

Glossary

FEDERAL POLICY (THE)	The federal policy that provides regulations for the involvement of human subjects in research. The policy applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency that takes appropriate administrative action to make the policy applicable to such research. Currently, sixteen federal agencies have adopted the Federal Policy. (Also known as the "Common Rule.")
FEDERAL REGISTER	The government's publication in which final and proposed rules or notices are published.
FETUS	The product of conception from the time of implantation until delivery.
FOOD AND DRUG ADMINISTRATION (FDA)	An agency of the federal government established by Congress in 1912 and presently part of the Department of Health and Human Services.
FULL IRB REVIEW	Review of proposed research at a convened meeting at which a majority of the membership of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. For the research to be approved, it must receive the approval of a majority of those members present at the meeting.
GENE THERAPY	The treatment of genetic disease accomplished by altering the genetic structure of either somatic (nonreproductive) or germline (reproductive) cells.
GENERAL CONTROLS	Certain FDA statutory provisions designed to control the safety of marketed drugs and devices. The general controls include provisions on adulteration, misbranding, banned devices, good manufacturing practices, notification and record keeping, and other sections of the Medical Device Amendments to the Food, Drug and Cosmetic Act.
GENETIC SCREENING	Tests to identify persons who have an inherited predisposition to a certain phenotype or who are at risk of producing offspring with inherited diseases or disorders.
GENOTYPE	The genetic constitution of an individual.
GRANT	Financial support provided for research study designed and proposed by the Principal Investigator(s). The granting agency exercises no direct control over the conduct of approved research supported by a grant. *Compare: Contract*

Glossary

GREATER THAN MINIMAL RISK	For the purposes of these SOPs and to accommodate the software used to document IRB procedures, studies considered to be more than minimal risk will be documented as High risk. (see Minimal Risk)
GUARDIAN	An individual who is authorized under applicable state or local law to give permission on behalf of a child to general medical care.
HIPAA AUTHORIZATION	The term HIPAA authorization means prior written permission for use and disclosure of protected health information (PHI) from the information's source person, research subject, or legally authorized personal representative, as required under law, including HIPAA. The written authorization must include all elements of a compliant authorization (see VHA Directive 1605.01) prior to any disclosure of information.
HISTORICAL CONTROLS	Control subjects (followed at some time in the past or for whom data are available through records) who are used for comparison with subjects being treated concurrently. The study is considered historically controlled when the present condition of subjects is compared with their own condition on a prior regimen or treatment.
HUMAN BIOLOGICAL SPECIMENS	Materials derived from human individuals, such as blood, urine, tissue, organs, hair, nail clippings, buccal swabs, or any other materials that are either collected specifically for research purposes or as residual specimens from diagnostic, therapeutic, or surgical procedures. Bacteria, fungi, or viruses obtained from human biological specimens are not considered human biological specimens, as long as the human material has been removed.
HUMAN IN VITRO FERTILIZATION	Any fertilization involving human sperm and ova that occurs outside the human body.
HUMAN RESEARCH	Human research is research involving human subjects as defined in this Handbook or research involving one or more identifiable human biological specimens.
HUMAN RESEARCH PROTECTIONS COORDINATOR	An individual who has responsibility for day-to-day operation and implementation of the institution's program for protecting human subjects. The Human Protections Coordinator should have detailed knowledge of institutional protection mechanisms and be readily available for consultation with federal officials and institutional personnel. The IRB

	Chairperson should not serve as the Human Protections Coordinator.
HUMAN RESEARCH PROTECTION PROGRAM (HRPP)	An HRPP is a comprehensive system to ensure the protection of human subjects participating in research. The HRPP consists of a variety of individuals and committees such as: the Medical Center Director, Associate Chief of Staff (ACOS) for Research and Development (R&D), the Administrative Officer (AO) for R&D, compliance officers, etc., the R&D Committee, the IRB, other committees or subcommittees addressing human subjects protection (e.g., Biosafety, Radiation Safety, Radioactive Drug Research, Conflict of Interest), Investigators, IRB staff, research staff, health and safety staff (e.g., Biosafety Officer, Radiation Safety Officer) and research pharmacy staff. The objective of this system is to assist the institution in meeting ethical principles and regulatory requirements for the protection of human subjects in research.
HUMAN STUDIES SUBCOMMITTEE	The name for the Institutional Review Board at the Durham VAHCS. *See: Institutional Review Board.*
HUMAN SUBJECTS	Individuals whose physiologic or behavioral characteristics and responses are the object of study in a research project. Under the federal regulations, human subjects are defined as: living individual(s) about whom an Investigator conducting research obtains: (1) data through intervention or interaction with the individual; or (2) identifiable private information. [45 CFR 46.102(f)] NOTE: FDA's regulations define human subject as an individual (they do not use the adjective "living) who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient [21 CFR 50.3(g) and 56.102(e)]." VA's definition: A human subject is a living individual about whom an Investigator conducting research obtains data through intervention or interaction with the individual or through identifiable private information (38 CFR 16.102(f)). The definition provided in the Common Rule includes Investigators, technicians, and others assisting Investigators, when they serve in a "subject" role by being observed, manipulated, or sampled. As required by 38 CFR 16.102(f) an intervention includes all physical procedures by which data are gathered and all physical, psychological, or environmental manipulations that are performed for research purposes.
IDE	See: Investigational Device Exemptions.
IN VITRO	Literally, "in glass" or "test tube;" used to refer to processes that are carried out outside the living body, usually in the

	laboratory, as distinguished from in vivo.
IN VIVO	Literally, "in the living body;" processes, such as the absorption of a drug by the human body, carried out in the living body rather than in a laboratory (in vitro).
INCAPACITY	Refers to a person's mental status and means inability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Often used as a synonym for incompetence. (*See also: Incompetence*.)
INCLUSION CRITERIA	The criteria that establish whether a person is eligible to participate in a clinical trial.
INCOMPETENCE	Technically, a legal term meaning inability to manage one's own affairs. Often used as a synonym for incapacity. (*See also: Incapacity*.)
IND	See: Investigational New Drug.
INDEPENDENT ETHICS COMMITTEE (IEC)	The equivalent of an IRB under the International Conference on Harmonisation Guidelines for Good Clinical Practice.
INDIVIDUALLY IDENTIFIABLE	Individually identifiable refers to private information or specimens that can be linked to specific individuals by the Investigator(s) either directly or indirectly through coding systems. Private information or specimens are not considered to be individually identifiable when they cannot be linked to specific individuals by the Investigator(s) either directly or indirectly. For research covered by HIPAA privacy regulations, research information comprising protected health information will be considered not to be individually identifiable if it does not contain any identifiers in accordance with HIPAA standards.
INFORMATION, PRIVATE	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). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the Investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.
INFORMED CONSENT	A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic,

	therapeutic, or preventive procedure.
INSTITUTION	Any public or private entity or agency (including federal, state, and local agencies). VA's definition: In the context of the VHA an institution is a VA medical center or integrated VA health care system and its satellite facilities including community-based outpatient clinics.
INSTITUTIONAL OFFICIAL (IO)	The IO is the Medical Center Director. The IO is the VA official responsible for ensuring that the HRPP at the facility has the resources and support necessary to comply with all federal regulations and guidelines that govern human subjects' research. The IO is legally authorized to represent the institution, is the signatory official for all Assurances, and assumes the obligations of the institution's Assurance. The IO is the point of contact for correspondence addressing human subjects' research with OHRP, FDA, and VA Central Office.
INSTITUTIONAL REVIEW BOARD (IRB)	A specially constituted review body established or designated by an entity to protect the welfare of human subjects recruited to participate in biomedical or behavioral research.
INSTITUTIONALIZED COGNITIVELY IMPAIRED	Persons who are confined, either voluntarily or involuntarily, in a facility for the care of the mentally or otherwise disabled (*e.g.*, a psychiatric hospital, home, or school for the retarded).
INSTITUTIONALIZED	Confined, either voluntarily or involuntarily (*e.g.*, a hospital, prison, or nursing home).
INTERACTION	In the context of research, interaction includes communication (including conversations, monitoring, gathering, or recording of data that occurs via telephone, e-mail, or other electronic device) or interpersonal contact between the Investigator, or member of the research staff, or other individual who is gathering and recording data for a research study.
INTERVENTION	In research, intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
INVESTIGATIONAL DEVICE	As defined by the FDA, an investigational device is a device that is the object of a clinical study designed to evaluate the safety or effectiveness of the device (21 CFR 812.3(g)). Investigational devices include transitional devices (21 CFR 812.3(r)) that are objects of investigations. However, for the

	purposes of this VHA Handbook, an investigational device may be an approved device that is being studied for an unapproved use or efficacy.
INVESTIGATIONAL DEVICE EXEMPTIONS (IDE)	An IDE is an application to FDA that allows an investigational significant risk device to be used in a clinical investigation to collect safety and effectiveness data. If the device is a non-significant risk device, it is considered to have an approved application for IDE after IRB approval is obtained (see 21 CFR 812).
INVESTIGATIONAL NEW DRUG (IND) OR DEVICE (IDE)	A drug or device permitted by FDA to be tested in humans but not yet determined to be safe and effective for a particular use in the general population and not yet licensed for marketing. For the purposes of the VHA, an Investigational Drug may be an approved drug that is being studied for an unapproved or approved use in a controlled, randomized or blinded clinical trial.
INVESTIGATIONAL NEW DRUG APPLICATION (IND)	An application to conduct a clinical investigation involving a drug not yet determined by the Food and Drug Administration to be safe and effective for a particular use in the general population and not yet licensed for marketing [21 CFR 312.1].
INVESTIGATOR	An Investigator is any individual who conducts research involving human subjects including, but not limited to, the PI, co-PI, and Local Site Investigator (LSI). The Investigator must uphold professional and ethical standards and practices, adhere to all applicable Federal requirements, and comply with applicable local policies and procedures. (1) **VA Investigator**. A VA Investigator is any individual who conducts research approved by the VA R&D committee while acting under a VA appointment on VA time, including full and part-time employees, without compensation (WOC) employees, and individuals appointed or detailed to VA under the Intergovernmental Personnel Act (IPA) of 1970. In addition, a VA Investigator must comply with all applicable VA and VHA requirements, and comply with applicable local VA facility policies and procedures. (2) **Principal Investigator (PI)**. The PI is a qualified person or persons designated by an applicant institution to direct a research project or program and who usually writes the grant application. The PI oversees scientific, technical, and day-to-day management of the research. In the event of an investigation conducted by a team of individuals, the PI is the

	responsible leader of that team. ***NOTE:*** *FDA considers Investigator and PI to be synonymous.* (3) **Co-Principal Investigator (Co-PI).** A Co-PI is when one of two or more PIs share equally in the accountability for a study. A Co-PI must meet the same qualifications of a PI. (4) **Site Investigator or Local Site Investigator (LSI).** The Site Investigator or LSI is an Investigator at a site participating in a multi-site research project. The LSI oversees scientific, technical, and day-to-day management of the research at the local site.
IONIZING RADIATION	Ionizing radiation is particles or rays with sufficient energy to cause the ejection of orbital electrons from absorber atoms. Ionizing radiation should be addressed within the protocol and the informed consent when its use is part of the research study. Ionizing radiation includes diagnostic and therapeutic procedures done for research purposes. Sources of radiation include: nuclear medicine, radiation therapy, and radiology.
IRB	See: Institutional Review Board.
IRB RECORDS	IRB records include but are not limited to: all minutes of IRB meetings, a copy of all proposals reviewed including all amendments, Investigator brochures, any supplemental information including recruitment and informational materials, consent forms, information submitted for continuing review, all correspondence, and IRB membership with a resume for each member. (See definition of Research Record).
JUSTICE	An ethical principle discussed in the Belmont Report requiring fairness in distribution of burdens and benefits; often expressed in terms of treating persons of similar circumstances or characteristics similarly.
LEGALLY AUTHORIZED REPRESENTATIVE (LAR)	A LAR is an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research (38 CFR 16.102(c)).
LONGITUDINAL STUDY	A study designed to follow subjects forward through time.
MEDICAL DEVICE	A diagnostic or therapeutic article that does not achieve any of its principal intended purpose through chemical action within or on the body. Such devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intraocular lenses, and orthopedic pins or other orthopedic equipment.

Glossary

MEMBER	A person who is listed on the roster of an IRB as a voting participant in IRB deliberations and actions.
MENTALLY DISABLED	See: Cognitively Impaired.
MINIMAL RISK	A risk is minimal 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. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination. The following definition of minimal risk for research involving prisoners differs somewhat from that given for non-institutionalized adults. 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 [45 CFR 46.303(d)].
MONITORING	A mechanism for keeping track of any part of the research process: data analysis, recruitment of subjects, informed consent process, to ensure its compliance with Institutional Review Board dictates and the federal regulations.
NATIONAL COMMISSION	National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. An interdisciplinary advisory body, established by Congressional legislation in 1974, which was in existence until 1978, and which issued a series of reports and recommendations on ethical issues in research and medicine, many of which are now embodied in federal regulations.
NEW DRUG APPLICATION	Request for FDA approval to market a new drug.
NIH	National Institutes of Health: a federal agency within the Public Health Service, DHHS, comprising 21 institutes and centers. It is responsible for carrying out and supporting biomedical and behavioral research.
NONAFFILIATED MEMBER	IRB Member who has no ties (and whose immediate family members have no ties) to the parent institution, its staff, or faculty. This individual is usually from the local community (*e.g.*, minister, business person, attorney, teacher, homemaker) [45 CFR 46.107(d) and 21 CFR 56.107(d)].

Glossary

NONCOMPLIANCE	Any failure to adhere to the requirements for conducting VA research covered by VHA Handbook 1058.01
NON-SCIENTIST	Member of an IRB who does not have a scientific background, but may be affiliated with the institution [45 CFR 46.107(c); and 21 CFR 56.107(c)]. At least one non-scientist member must be present at convened meetings to approve research [45 CFR 46.108(b) and 21CFR 46.108(c)].
NONSIGNIFICANT RISK DEVICE	An investigational medical device that does not present significant risk to the patient. (*See also: Significant Risk Device*.)
NONTHERAPEUTIC RESEARCH	Research that has no likelihood or intent of producing a diagnostic, preventive, or therapeutic benefit to the current subjects, although it may benefit subjects with a similar condition in the future.
NORMAL VOLUNTEERS	Volunteer subjects used to study normal physiology and behavior or who do not have the condition under study in a particular protocol, used as comparisons with subjects who do have the condition. "Normal" may not mean normal in all respects. For example, patients with broken legs (if not on medication that will affect the results) may serve as normal volunteers in studies of metabolism, cognitive development, and the like. Similarly, patients with heart disease but without diabetes may be the "normals" in a study of diabetes complicated by heart disease
NOTICE of PROPOSED RULE-MAKING (NPRM)	Pursuant to the Administrative Procedure Act, the government must typically issue a notice of a proposed rule before it issues the final rule. This affords the public the opportunity to comment on contemplated government action.
NUREMBERG CODE	A code of research ethics developed during the trials of Nazi war criminals following World War II and widely adopted as a standard during the 1950s and 1960s for protecting human subjects.
OFFICE FOR HUMAN RESEARCH PROTECTIONS (OHRP)	The office within the Department of Health and Human Services, responsible for implementing DHHS regulations (45 CFR Part 46) governing the protection of human subjects in research.
OFFICE FOR PROTECTION FROM RESEARCH RISKS (OPRR)	Until June 2000, this office was within the DHHS as part of the National Institutes of Health (NIH). OPRR was responsible for the implementation of the DHHS regulations [45 CFR Part 46] governing research involving human subjects. The Office for Human Research Protections supersedes OPRR.

Glossary

OFFICE OF RESEARCH AND DEVELOPMENT (ORD)	ORD is the office within VA Central Office responsible for the overall policy, planning, coordination, and direction of research activities within VHA. ***NOTE:*** *The Research Integrity Development and Education Program (PRIDE) is the program within ORD that is responsible for training, education, and policy development related to human subjects protection.*
OFFICE OF RESEARCH OVERSIGHT (ORO)	ORO is the primary VHA office for advising the Under Secretary for Health on all matters regarding compliance and oversight of research in the protection of human subjects, animal welfare, and research safety. ORO oversees investigations of allegations of research misconduct.
ORAL CONSENT	Typically refers to informed consent that is obtained from a subject without use of a written informed consent document.
PARENTAL PERMISSION	The agreement of one or both parents or a guardian to research involving a minor (45 CFR 46.402(c)].
PATERNALISM	Making decisions for others against or apart from their wishes with the intent of doing them good.
PERMISSION	The agreement of parent(s) or guardian to the participation of their child or ward in research.
PHARMACOLOGY	The scientific discipline that studies the action of drugs on living systems (animals or human beings).
PHASE 1 TRIALS	Includes the initial introduction of an investigational new drug into humans. These studies are typically conducted with healthy volunteers; sometimes, where the drug is intended for use in patients with a particular disease, however, such patients may participate as subjects. Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase 1 trials is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled, sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. The

	total number of subjects involved in Phase 1 investigations is generally in the range of 20-80.
PHASE 1, 2, 3, 4 DRUG TRIALS	Different stages of testing drugs in humans, from first application in humans (Phase 1) through limited and broad clinical tests (Phases 2 and 3), to postmarketing studies (Phase 4).
PHASE 2 TRIALS	Includes controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well controlled, closely monitored, and conducted with a relatively small number of patients, usually involving no more than several hundred subjects [21 CFR 312.21(a)].
PHASE 3 TRIALS	Involves the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, efficacy, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug, and to provide an adequate basis for physician labeling. In Phase 3 studies, the drug is used the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to the FDA for approval to market the drug. Phase 3 trials usually involve several hundred to several thousand patient-subjects [21 CFR 312.21(c)].
PHASE 4 TRIALS	Studies conducted after a drug has been approved by FDA, to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time [21 CFR 312.85].
PILOT STUDY	Pilot studies are full-fledged research studies that must be approved by the IRB(s), when human subjects are involved. They are not considered to be activities preparatory to research.

Glossary

PLACEBO	In biomedical research, a chemically inert substance used in the guise of treatment for its psychologically suggestive effect; used in controlled clinical trials as a comparator to determine whether improvement and side effects may reflect imagination or anticipation rather than the actual power of a drug. In social and behavioral research, a condition that mimics the experimental context but does not include the experimental manipulation under study. As in biomedical research, the control condition is used to confirm that observed effects are the result of the experimental manipulation rather than the research context itself.
PREGNANCY	The period of time from confirmation of implantation of a fertilized egg within the uterus until the fetus has entirely left the uterus (*i.e*., has been delivered). Implantation is confirmed through a presumptive sign of pregnancy such as missed menses or a positive pregnancy test. This "confirmation" may be in error, but, for research purposes, Investigators would presume that a living fetus was present until evidence to the contrary was clear. Although fertilization occurs a week or more before implantation, the current inability to detect the fertilization event or the presence of a newly fertilized egg makes a definition of pregnancy based on implantation necessary.
PREMARKET APPROVAL (PMA)	Process of scientific and regulatory review by the FDA to ensure the safety and effectiveness of Class III devices.
PREPARATORY TO RESEARCH	Within VHA, activities “preparatory to research” refer to activities that are necessary for the development of a specific protocol. PHI from data repositories or medical records may be reviewed during this process without IRB approval, subject authorization, or a waiver of authorization, but only aggregate data may be recorded and used in the protocol application (e.g., potential number of subjects meeting study criteria at each site). Within VHA, an activity preparatory to research does <u>not</u> include the identification of potential subjects and recording of data for the purpose of recruiting these subjects or to link with other data. The preparatory to research activity ends once the protocol has been submitted to the IRB for review (see VHA Handbook 1200.12).
PRESIDENT'S COMMISSION	President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. An interdisciplinary advisory group, established by congressional legislation in 1978, which was in existence until 1983, and

	which issued reports on ethical problems in health care and in research involving human subjects.
PRINCIPAL INVESTIGATOR	See: Investigator.
PRISONER	An individual involuntarily confined in a penal institution, including persons: (1) sentenced under a criminal or civil statue; (2) detained pending arraignment, trial, or sentencing; and (3) detained in other facilities (*e.g.*, for drug detoxification or treatment of alcoholism) under statutes or commitment procedures providing such alternatives to criminal prosecution or incarceration in a penal institution [45 CFR 46.303(c)]. The definition of minimal risk for research involving prisoners differs somewhat from that given for non-institutionalized adults.
PRISONER REPRESENTATIVE	A member of an IRB who has appropriate background and experience to represent the interests and concerns of an individual who is involuntarily confined to an institution [45 CFR 46.304 (b)].
PRIVACY	Control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others.
PRIVATE INFORMATION	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). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the Investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects (38 CFR 16.102(f)).
PROBAND	The person whose case serves as the stimulus for the study of other members of the family to identify the possible genetic factors involved in a given disease, condition, or characteristic.
PROPHYLACTIC	Preventive or protective; a drug, vaccine, regimen, or device designed to prevent, or provide protection against, a given disease or disorder.
PROSPECTIVE STUDIES	Studies designed to observe outcomes or events that occur subsequent to the identification of the group of subjects to be studied. Prospective studies need not involve manipulation or intervention but may be purely observational or involve only the collection of data.
PROTOCOL	The formal design or plan of an experiment or research activity; specifically, the plan submitted to an IRB for review and to an agency for research support. The protocol

	includes a description of the research design or methodology to be employed, the eligibility requirements for prospective subjects and controls, the treatment regimen(s), and the proposed methods of analysis that will be performed on the collected data.
PROTOCOL DEVIATION	Any departure, alteration, or procedural error in the IRB approved protocol and/or study procedures that occurs without prior IRB notification and approval.
QUORUM	A quorum is defined as a majority of the voting members as listed on the IRB membership. In the case of the IRB, a quorum must include at least one member whose primary concerns are in non-scientific areas. At meetings of the IRB, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote.
RANDOM RANDOM ASSIGNMENT RANDOMIZATION RANDOMIZED	Assignment of subjects to different treatments, interventions, or conditions according to chance rather than systematically (*e.g.*, as dictated by the standard or usual response to their condition, history, or prognosis, or according to demographic characteristics). Random assignment of subjects to conditions is an essential element of experimental research because it makes more likely the probability that differences observed between subject groups are the result of the experimental intervention.
RECOMBINANT DNA TECHNOLOGY	DNA resulting from the insertion into the chain, by chemical or biological means, of a sequence (a whole or partial chain of DNA) not originally (biologically) present in that chain. Recombinant DNA technology is also used to develop diagnostic screens and tests, as well as drugs and biologics for treating diseases with genetic components.
RECRUITMENT	The process of enrolling human subjects in research protocols.
RECUSE	To disqualify (oneself) as judge in a particular case; *broadly*: to remove (oneself) from participation to avoid a conflict of interest.
REMUNERATION	Payment that will be given to subjects who volunteer to participate in research. (*Compare: Compensation*.)
RESEARCH	Research is a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge [45 CFR 46.102(d)]. Any

	experiment that involves a test article and one or more human subjects and that either is subject o requirements for prior submission to the FDA under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit. [21 CFR 50.3 (c) It evaluates the safety or effectiveness of a medical device (21 CFR 812.2(a)). This is the meaning of "experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act."A research project generally is described in a protocol that sets forth explicit objectives and formal procedures designed to reach those objectives. VA's definition: Research is defined 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. The Common Rule (38 CFR 16) defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge. **NOTE:** The FDA definition of research differs according to the applicable regulations; see 21 CFR 812.3(h), 21 CFR 50.3(c), 21 CFR 56.102(c), and 21 CFR 312.3(b).
RESEARCHER	A researcher is the PI and/or Investigator.
RESEARCH & DEVELOPMENT COMMITTEE (R&D)	The committee within the VA responsible for maintaining high standards in research review that assures the scientific quality of the R&D projects, protections of human rights, laboratory safety, and welfare of animal subjects in research and development. The R&D committee is the parent committee of the IRB. All R&D activities within the facility, whether funded or unfunded, are within its purview.
Research Misconduct	Fabrication, falsification or plagiarism in proposing, performing or reviewing research or reporting research results. See VHA Handbook 1058.02
RESEARCH RECORDS	Research records include, but are not limited to, IRB and R&D Committee records, records of all observations, other data relevant to the investigation, progress notes, research study forms, surveys, questionnaires, and other documentation

	regarding the study (VHA Handbook 1907.01). (1) **IRB Records.** IRB records include, but are not limited to: copies of all research proposals and amendments reviewed; scientific evaluations, if any, that accompany the proposals; approved informed consent documents; progress reports submitted by Investigators; reports of injuries to subjects; reports of complaints from subjects; minutes of IRB meetings; reports of expedited review activities; records of continuing review activities; copies of all correspondence between IRB and the Investigators; reports of deviations from IRB-approved protocol; a list of IRB members; written procedures for IRB in the same detail as described in 38 CFR 16.103(b)(4) and (5); and statements of significant new findings provided to subjects as required by 38 CFR 16.116(b)(5). (2) **Investigators' Research Records**. Research records include the following when relevant to the study: copies of all IRB-approved versions of the protocol and amendments; case report forms and supporting data (including but not limited to signed and dated informed consent forms and HIPAA authorization forms); documentation on each subject including informed consent, interactions with subjects by telephone or in person, observations, interventions, and other data relevant to the research study; reports of adverse events; data analyses; codes and keys used to de-identify and re-identify subjects' PHI; reports (including, but not limited to abstracts and other publications); all correspondence (including, but not limited to, that with the funding source or sponsor) and with applicable oversight entities (including, but not limited to, IRB, R&D Committee, ORO, and FDA).
RESPECT FOR PERSONS	An ethical principle discussed in the Belmont Report requiring that individual autonomy be respected and that persons with diminished autonomy be protected.
RETROSPECTIVE STUDIES	Research conducted by reviewing records from the past (*e.g.*, birth and death certificates, medical records, school records, or employment records) or by obtaining information about past events elicited through interviews or surveys.
REVIEW (OF RESEARCH)	The concurrent oversight of research on a periodic basis by an IRB. In addition to the at least annual reviews mandated by the federal regulations, reviews may, if deemed appropriate, also be conducted on a continuous or periodic basis.

Glossary

RISK	The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant. Federal regulations define only "minimal risk." (*See also: Minimal Risk*.)
SECRETARY	In the context of the federal regulations pertaining to the protection of human subjects in research, refers to the head of a federal agency [45 CFR 46.102(a)].
SCIENTIFIC REVIEW GROUP	A group of highly regarded experts in a given field, convened by NIH to advise NIH on the scientific merit of applications for research grants and contracts. Scientific review groups are also required to review the ethical aspects of proposed involvement of human subjects. Various kinds of scientific review groups exist, and are known by different names in different institutes of the NIH (*e.g.*, Study Sections, Initial Review Groups, Contract Review Committees, or Technical Evaluation Committees).
SENSITIVE INFORMATION	VA sensitive information is all department data, on any storage media or in any form or format, which requires protection due to the risk of harm that could result from inadvertent or deliberate disclosure, alteration, or destruction of the information. The term includes information whose improper use or disclosure could adversely affect the ability of an agency to accomplish its mission; proprietary information; records about specific individuals requiring protection under various confidentiality provisions, such as the Privacy Act and the HIPAA Privacy Rule; and information that can be withheld under the Freedom of Information Act (see VA Directive 6500 and VA Handbook 6500).
SERIOUS ADVERSE EVENT (SAE)	A local SAE in human research is an AE that results in death, a life threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect. An AE is also considered serious when medical, surgical, behavioral, social, or other intervention is needed to prevent such an outcome.
SIGNIFICANT RISK DEVICE	An investigational medical device that presents a potential for serious risk to the health, safety, or welfare of the subject.
SITE VISIT	A visit by agency officials, representatives, or consultants to the location of a research activity to assess the adequacy of IRB protection of human subjects or the capability of personnel to conduct the research.

Glossary

SPONSOR	For FDA studies, the FDA considers a sponsor to be the person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual, pharmaceutical company, governmental agency, academic institution, private organization, or other. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-Investigator. A person other than an individual that uses one or more of their own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-Investigator, and the employees are Investigators (21 CFR 312.3 and 21 CFR 812.3).
SPONSOR-INVESTIGATOR	An individual who both initiates and actually conducts, alone or with others, a clinical investigation. Corporations, agencies, or other institutions do not qualify as Sponsor-Investigators.
STATISTICAL SIGNIFICANCE	A determination of the probability of obtaining the particular distribution of the data on the assumption that the null hypothesis is true. Or, more simply put, the probability of coming to a false positive conclusion. If the probability is less than or equal to a predetermined value (*e.g.*, 0.05 or 0.01), then the null hypothesis is rejected at that significance level (0.05 or 0.01).
SUBJECTS (HUMAN)	See: Human Subjects.
SUBCOMMITTEE ON HUMAN STUDIES	See: IRB
SUBPART A	The DHHS codification of the Federal Policy for the Protection of Human Subjects in Research is found in Subpart A of 45 CFR Part 46 (also known as The Common Rule).
SUBPART B	Subpart B of the DHHS regulations [45 CFR Part 46] contains additional protections for pregnant women and fetuses that are involved in research, and references human in vitro fertilization research.
SUBPART C	Subpart C of the DHHS regulations [45 CFR Part 46] contains additional protections for prisoners who are involved in research.
SUBPART D	Subpart D of the DHHS regulations [45 CFR Part 46] contains additional protections for children who are involved in research.
SURVEYS	Studies designed to obtain information from a large number of respondents through written questionnaires, telephone interviews, door-to-door canvassing, or similar procedures.
SUSPENSION	Typically used in the context of a federal agency taking action against an institution. For example, the Office for Human Research Protections can suspend an Assurance, preventing the institution from continuing studies supported with federal funds.

Glossary

SUSPENSION OF IRB APPROVAL	A suspension of IRB approval is a determination by the IRB Chair, a qualified IRB voting member designated by the IRB Chair, or the convened IRB to temporarily interrupt some or all previously-approved research activities. The suspended activities could include, but not be limited to, recruiting of new subjects for the research. Suspended studies remain open and require continuing review.
SYSTEMIC DEFICIENCY	A systemic deficiency is a fundamental, underlying problem that jeopardizes the effectiveness of the facility's research protection system (s).
TERMINATION OF IRB APPROVAL	A termination of IRB approval is a determination by the convened IRB to permanently halt some or all previously approved research activities including, but not limited to, enrollment of new subjects in research.
TEST ARTICLE	Any drug (including a biological product for human use), medical device for human use, or any other article subject to regulation by the Food and Drug Administration under 42 USC 262, 263b-263N. VA's definition: For purposes of this document, a test article is a drug, device, or other article including a biological product used in clinical investigations involving human subjects or their specimens.
TISSUE BANKING	See: Banked Specimens
THERAPEUTIC INTENT	The research physician's intent to provide some benefit to improving a subject's condition (*e.g.*, prolongation of life, shrinkage of tumor, or improved quality of life, even though cure or dramatic improvement cannot necessarily be affected.) This term is sometimes associated with Phase 1 drug studies in which potentially toxic drugs are given to an individual with the hope of inducing some improvement in the patient's condition as well as assessing the safety and pharmacology of a drug.
THERAPY	Treatment intended and expected to alleviate a disease or disorder.
UNDUE INFLUENCE	This refers to a prohibition in the Common Rule that Investigators not use unfair measure or influence to enroll persons in research [45 CFR 46.116].
UNANTICPATED PROBLEMS INVOLVING RISKS TO SUBJECTS or OTHERS	This is a regulatory phrase which requires reporting of this event to the IRB and to the government [45 CFR 46.103(d)(5); 21 CFR 56.108(b)]. An unanticipated problem is an event that is not expected given the nature of the research and subject population, and exposes subjects or others to a greater risk of harm or discomfort related to the research than was previously

	known or foreseen. Unanticipated problems can be adverse events but also include problems not considered to be adverse events.
UNEXPECTED/ UNANTICIPATED ADVERSE EVENT (UAE)	An UAE is an AE that is new or greater than previously known, in terms of nature, severity, or frequency of occurrence, as documented in the protocol or other materials approved by IRB. Such materials may include, but are not limited to: the informed consent form, clinical Investigator's brochure, and product labeling (see VHA Handbook 1058.01). ***NOTE:*** *For the purposes of this document, "unanticipated" is the same as "unexpected."*
UNEXPECTED/ UNANTICIPATED ADVERSE DEVICE EFFECT	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subjects (21 CFR 812.150(a).
USUAL CARE	Usual care is medical or other treatment or services a research subject would receive if not participating in the research study (e.g., the chemotherapy an oncology patient would receive whether or not the patient was participating in a research study).
VA-APPROVED RESEARCH	VA research is research that is approved by the R&D Committee and conducted by VA Investigators including PIs, Co-PIs, and Site Investigators on VA time (serving on compensated, WOC, or IPA appointments), utilizing VA resources (e.g., equipment), or on VA property including space leased to, and used by VA. The research may be funded by VA, by other sponsors, or be unfunded.
VA-SPONSORED TISSUE BANK	A tissue repository located at a VA facility or an approved off-site location that operates in accordance with established VA policies. The repository stores human biological specimens collected under VA-approved research protocols and are under VA ownership and VA control.
VACCINE	A biologic product generally made from an infectious agent or its components — a virus, bacterium, or other microorganism — that is killed (inactive) or live-attenuated (active, although weakened). Vaccines may also be

	biochemically synthesized or made through recombinant DNA techniques.
VARIABLE (NOUN)	An element or factor that the research is designed to study, either as an experimental intervention or a possible outcome (or factor affecting the outcome) of that intervention.
VOLUNTARY	Free of coercion, duress, or undue inducement. Used in the research context to refer to a subject's decision to participate (or to continue to participate) in a research activity.
VULNERABLE SUBJECTS	Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.
WAIVER OF INFORMED CONSENT	An action taken by the IRB permitting the Investigator to pursue research involving human subjects without obtaining informed consent [45 CFR 46.116(d)].
WAIVER OF DOCUMENTATION OF INFORMED CONSENT	An action taken by the IRB permitting the Investigator to pursue research involving human subjects without obtaining a signed consent form from some or all of the subjects for research that presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context, or when 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.(38 CFR 16.116(c).

Statement of Authority and Purpose

STATEMENT OF AUTHORITY AND PURPOSE

Introduction

The Durham VA Health Care System (VAHCS) Research Standard Operating Procedures (SOP) is a reference for IRB members, Investigators and research staff involved in the conduct of research. These SOPs detail the policies and procedures specifying the regulations and policies governing human subjects' research, and the requirements for submitting research proposals for review to the IRB and the Research and Development (R&D) Committee.

1. Ethical Principles Governing the IRB

Research at the Durham VAHCS must be carried out in an ethical manner (38 CFR16.103(b)(1). The basic ethical principles guiding research involving human subjects are provided in the Nuremberg Code and the Declaration of Helsinki. IRBs are guided by the ethical principles as set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, titled: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (the "Belmont Report"). Three basic principles contained in The Belmont Report are central to the ethics of research involving humans and guide the IRB in assuring that the rights and welfare of subjects are protected:

a) Beneficence – is applied so that possible benefits are maximized and possible risks are minimized to the persons involved.

b) Respect for persons – is applied by obtaining informed consent, through consideration of privacy, confidentiality, and additional protections for vulnerable populations. Informed consent is obtained, unless the requirements for waiver of informed consent are met by adequate and appropriate methods in accordance with the provisions of applicable regulations.

c) Justice – is evidenced by the equitable selection of subjects. The subject population is representative of the group that will benefit from the research.

2. Regulatory Mandate to Protect Human Subjects

Department of Veterans Affairs (VA) and other Federal regulations require specific protections for human subjects.

A. Department of Health and Human Services (DHHS) Regulations at 45 CFR 46 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm). In May of 1974, the Department of Health, Education, and Welfare (later renamed DHHS) codified its basic human subject protection regulations at 45 CFR 46, Subpart A. Revised in 1981 and 1991, the DHHS regulations presently include additional protections for fetuses, pregnant women, and human in vitro fertilization (Subpart B), prisoners (Subpart C),

and children (Subpart D). The DHHS regulations are enforced by the Office for Human Research Protections (OHRP).

B. Department of Veterans Affairs (VA) Regulations at 38 CFR 16 for the Protection of Human Subjects

In addition, 38 CFR 17.33 provides regulations for patient rights. 38 CFR 17.45 is Medical Hospital Care for Research Purposes. 38 CFR 17.92 is Outpatient Care for Research Purposes. In January of 1991, the VA joined 16 other Executive Branch Departments and Agencies in simultaneously adopting the Federal Policy (Common Rule) for the Protection of Human Subjects. The Federal Policy codified by the VA at 38 CFR 16, is the same as that codified by DHHS regulations at 45 CFR 46, but does not include the additional DHHS Subparts.

C. Food and Drug Administration (FDA) Regulations at 21 CFR 50 and 56

When DHHS revised its regulations in 1981, the FDA codified almost identical informed consent regulations at 21 CFR 50 and IRB regulations at 21 CFR 56. Additional FDA regulations that are relevant to the protection of human subjects are:

(1) Investigational New Drug Applications (IND) (21 CFR 312);

(2) Radioactive Drugs (21 CFR 361);

(3) Biological Products (21 CFR 600);

(4) Investigational Device Exemptions (IDE) (21 CFR 812);

(5) Additional Safeguards for Children (21CFR 50, Subpart D).

D. Department of Defense (DoD) Regulations at 32 CFR 219

Any human subject research conducted at Durham VAHCS and funded by the DoD will follow all applicable DoD rules, regulations, and directives.

E. Department of Education (ED) Regulations at 34 CFR and 343

Any human subject research conducted at Durham VAHCS and funded by the ED will follow all applicable ED rules, regulations, and directives.

3. Authority

A. Institutional Authority of the IRB (38 CFR 16.109)

The IO is the Medical Center Director (MCD). The MCD is responsible for all research activities conducted under medical center auspices. The IO is the VA official responsible for ensuring that the HRPP at the facility has the resources and support necessary to comply with all federal regulations and guidelines that govern human subjects' research. This includes making provisions for meeting space and sufficient staff to support the IRB's review and recordkeeping duties. The IO is legally authorized to represent the institution, is the signatory official for all Assurances, and assumes the obligations of the institution's Assurance. The MCD is responsible for ensuring that the IRB functions

independently, and that the IRB Chairperson(s) and IRB members have direct access to the IO for appeal if they experience undue influence or if they have concerns about the IRB. The MCD is responsible for ensuring that the Durham VAHCS maintains accreditation with an organization approved by ORD to perform this function. This accreditation must be obtained and maintained in accordance with a schedule determined by ORD. The MCD and the Research and Development (R&D) Committee, who reports to the Director through the Chief of Staff, oversees the IRB. The MCD oversees all researchers and research staff. The IRB is a formally established subcommittee of the R&D Committee. The Durham VAHCS has one IRB of record registered with OHRP to review its human subject research. The IRB is an appropriately constituted group formally designated to review and monitor research involving human subjects to protect the rights and welfare of the subjects. The IRB also provides oversight and monitoring of such protections. In accordance with the Common Rule, VA and FDA regulations, the IRB has responsibility for approving, requiring modification (to secure approval), or disapproving research. The ACOS/R&D is responsible for implementation of the HRPP at the Durham VAHCS.

B. The Assurance and IRB Registration Process (38 CFR 16.103(a))

The Durham VAHCS's IRB is established and empowered under the auspices of the Institution's executive authorities, and by the Institution's Federal Wide Assurance with the federal Office for Human Research Protections. This Institution requires that all research projects involving humans as subjects or human material be reviewed and approved by the IRB prior to initiation of any research related activities, including recruitment and screening activities.

An assurance is a formal written, binding commitment that is submitted to a federal agency in which an institution promises to comply with applicable regulations governing research with human subjects and stipulates the procedures through which compliance will be achieved. VA's definition: An Assurance is also called an Assurance of Compliance, or a Federal-wide Assurance (FWA). It is a written commitment by an institution to protect human subjects participating in research. Under federal regulations, any institution conducting or engaged in federally supported research involving human subjects must obtain an Assurance in accordance with 38 CFR 16.103. ***NOTE****: All research conducted under VA auspices is considered to be Federally-supported.* This requirement also applies to any collaborating "performance site" institutions. Under 38 CFR 16.102(f), an institution is engaged in human subject research whenever its employees or agents: intervene or interact with living individuals for research purposes; or obtain, release, or access individually-identifiable private information for research purposes. An institution is automatically considered 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. An agent of the Durham VAHCS includes employees who are 1) compensated by the VA and have a VA appointment; 2) appointed to work without compensation (WOC); or 3) assigned to VA through the Intergovernmental Personnel Act (IPA). Contractors are not considered agents of the VA. Assurances are filed through the VA Office of Research Oversight (ORO) with the Department of Health and

Human Services (DHHS) Office for Human Research Protections (OHRP). The FWA replaces previous types of OHRP and VA assurances.
The IRB is established to review biomedical and behavioral research involving human subjects regardless of the source of funding and location of the study. Except for research in which the only involvement of humans is in one or more of the categories exempted or waived under 38 CFR 16 Section 101(b)(1-6) or 101(i), all research involving human subjects, and all other activities which even in part involve such research, regardless of sponsorship, are subject to these policies and procedures if one or more of the following apply:

1. The research is sponsored by institutional authorities and/or;
2. The research is conducted by or under the direction of any employee, staff, student or agent of the Institution in connection with his or her institutional responsibilities; and/or
3. The research is conducted by or under the direction of any employee, staff, student or agent of the Institution using any property or facility of the Institution; and/or the research involves the use of the Institution's nonpublic information to identify or contact human research subjects.

C. The Authority of the IRB (38 CFR 16, 17; 21 CFR 50, 56; and 45 CFR 46 (Appendix D))
The IRB, designated by the Durham VAHCS Director and the R&D Committee (VHA Handbook 1200.1), and named in the FWA must prospectively review and make a decision concerning all human subject research conducted at the Durham VAHCS or by Durham VAHCS employees or agents, or otherwise under the auspices of the VA. The use of a commercial IRB is prohibited (VHA Handbook 1200.05 ¶5). The Durham VAHCS IRB cannot serve as an IRB of record for any non-VA entity except for DOD facility or VA nonprofit research and education foundation. VA nonprofit research and education foundations must have an IRB of record of a VA facility. The Durham VAHCS IRB is the IRB of record for the non-profit Institute for Medical Research (IMR). Durham VAHCS does not rely upon or act as the IRB of record for another VHA entity. The IRB has the authority to ensure that research is designed and conducted in such a manner that protects the rights and welfare of participating subjects. Specifically:

1. The IRB may disapprove, modify or approve studies based upon consideration of human subject protection aspects;
2. The IRB reviews, and has the authority to approve, require modification in, or disapprove, all research activities that fall within its jurisdiction;
3. The IRB has the authority to conduct continuing review as it deems necessary to protect the rights and welfare of research subjects, including requiring progress reports from the Investigators and auditing the conduct of the study, observing or have a third party observe the informed consent process, and auditing the progress of any study under its jurisdiction as it deems necessary to protect the rights and welfare of human subjects;
4. The IRB may suspend or terminate approval of a study; and
5. The IRB may place restrictions on a study.

Regarding federally funded research, if the study is part of an application to the VA or a federal sponsoring agency, the human protocol must undergo preliminary review and receive concurrence from the R&D Committee (i.e., just-in-time) before the application is processed and receive final approval by the IRB and R&D prior to expenditure of any grant funds.

Although the IRB is a subcommittee of the R&D Committee (VHA Handbook 1200.1), neither the Director nor the R&D Committee can approve research involving human subjects that has not been approved by the IRB of record [38 CFR 116.112; VHA Handbook 1200.1¶10.g.]. If in the course of its review, the R&D Committee requires changes to the protocol that relate to the determination of the protection of the human subjects, the R&D Committee must refer those changes back to the IRB for its approval before the R&D Committee can give final approval.

4. Responsibility

A. IRB Review of Research

All research involving human subjects (as defined below), and all other activities, which even in part involve such research, regardless of sponsorship, must be reviewed and approved by the IRB and R&D Committee. No intervention or interaction with human subjects in research, including recruitment, may begin until the R&D Committee has reviewed and approved the research protocol and the Investigator has been notified in writing by the Associate Chief of Staff for Research & Development (ACOS/R&D) of the final approval. Final written notification will be provided to Investigators post R&D Committee review and approval. All responses to Subcommittee on Research Safety (SRS) recommendations must be approved prior to final R&D approval. Specific determinations as to the definition of “research” or “human subjects,” and their implications for the jurisdiction of the IRB under Institutional policy are determined by the IRB.

Classified research**: (** Research which is restricted to individuals with United States government security clearances) involving human subjects cannot be approved by a VA IRB or R&D Committee or performed at a VA facility, including space leased to, and used by VA.

Definition of Human Subject and Research (45 CFR 46.102(d), 38 CFR 16.102; VHA Handbook 1200.05)

Activities are human subject research under the Common Rule when they meet the DHHS definition of research.

Any systematic investigation (including research development, testing and evaluation) designed to develop or contribute to generalizable knowledge. The Durham VAHCS defines “systematic investigation” as a research activity that uses an organized approach to develop generalizable knowledge. It follows a defined set of steps and procedures and is designed to answer a question or test a hypothesis that addresses research intent. The Durham VAHCS defines “generalizable knowledge” as knowledge

that is collected under systematic procedures that can be applied to populations and/or settings different from the ones from which it was collected. VA regulations at 38 CFR 16.102(d) and VHA Handbook 1200.05 defines research as a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy. All research involving human subjects and all other activities, which even in part involve such research, regardless of sponsorship, must be reviewed and approved by the Durham VAHCS's IRB. No intervention or interaction with human subjects in research, including recruitment, may begin until the Research and Development Committee (R&D) has reviewed and approved the research protocol.

VA and DHHS regulations at 38 CFR 16.102(f) and 45 CFR 46.102(f) define human subject as "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. 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 (e.g., medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the Investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects."

Activities meeting the following criteria are considered human subjects research as defined by the FDA regulations

- Activity that involves research as defined by the FDA at 21 CFR §50.3(c),§56.103 (c), §312.3(b), or §812.3(h), and
- Activity that involves human subjects as defined by FDA at 21 CFR §50.3(g), §56.103(e), §56.312(b),§812.3(p).

An activity is FDA-regulated research when:

- It involves any use of a drug other than the use of an approved drug (approved by FDA for marketing) in the course of medical practice (21 CFR 312.3(b)). This is the meaning of "experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act" in the definition of "clinical investigation."
- It evaluates the safety or effectiveness of a medical device (21 CFR 812.2(a)). This is the meaning of "experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act."
- The results of the activity are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.

Statement of Authority and Purpose

Per 21 CFR 50(g), define human subject as an individual who becomes a participant in research, either a recipient of the test article or as a control. A subject may be either a healthy human or a patient. NOTE: FDA's regulations define human subject as an individual (they do not use the adjective "living") who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient [21 CFR 50.3(g) and 56.102(e)]." 21 CFR 50(c) define clinical investigation as any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the FDA under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

The following activities require Investigators to report emergency use to the IRB in five working days, and any subsequent use of the test article is subject to IRB review:

- Emergency use of an investigational drug, device, or biologic under 21 CFR §56.104(c) and 21 CFR §50.23(c)
- Humanitarian device use under 21 CFR §814.3(n) and 814.124

Participants at the Durham VAHCS must be either a healthy adult (>/=18yo) individual or an adult patient with or without decision making capabilities.

An IRB's primary responsibility is to ensure that the rights and welfare of subjects are protected in the Durham VAHCS human subject research program (38 CFR 16.109). In doing so, the designated IRB must ensure that the human subject research is conducted ethically, and in compliance with VA and other Federal regulations, the requirements of applicable state law, the VAHCS's FWA, the Non-profit Assurance, and the Durham VAHCS's institutional policies and procedures and other pertinent guidelines.

The IRB accomplishes prospective and continuing review of the Durham VAHCS's human subject research. This includes review of the protocol, the informed consent process, and procedures used to enroll subjects. In order to approve research, the IRB must review the full proposal, the consent form and all supplemental information such as but not limited to the Investigator's brochure and recruiting information. The IRB must determine that all of the following requirements are satisfied both initially and continually:

1) Risks, both physical and non-physical to human subjects are minimized;
2) Risks, both physical and non-physical to human subjects are reasonable in relation to any anticipated benefits;
3) Equitable selection of subjects;
4) Informed consents are reviewed and approved;
5) Informed consent is sought and the process documented on each prospective subject;
6) Adequate provisions for monitoring of data to ensure safety of subjects;
7) Adequate provisions are in place to protect the privacy and maintain the confidentiality of subject data;

8) Additional safeguards are in place to protect the welfare of vulnerable subjects;
9) Steps are taken to manage, reduce, or eliminate potential or real conflicts of interest; and
10) Investigators have met all current human subjects' educational requirements.

North Carolina State Statutory Structure Regarding Clinical Trials
North Carolina explicitly adopts federal requirements (45 CFR 46, or the Common Rule) to govern clinical trials, and does not otherwise impose significant state-specific standards for clinical trials or informed consent. North Carolina does impose special rules that mandate insurance coverage for cancer-related clinical trials.

Types of Human Subject Research and IRB Considerations
According to VA and federal regulations, the activities that require IRB review include any activities involving the collection of data through intervention or interaction with a living individual, or involving identifiable private information regarding a living individual. The following examples illustrate common types of human subject research. These are examples only, and are not exhaustive of all human subject research conducted at the Durham VAHCS.

1. **Clinical Research.** Clinical research involves research: (a) to increase scientific understanding about normal or abnormal physiology, disease states, or development and (b) to evaluate the safety, effectiveness or usefulness of a medical product, procedure, or intervention. Vaccine trials, medical device research, and cancer research are all types of clinical research. As defined in the FDA regulations, clinical investigation means any experiment that involves a test article and one or more human subjects. (21 CFR 56.102) The terms research, clinical research, clinical study, and clinical investigation are generally considered to be synonymous.

2. **Behavioral and Social Sciences Research.** The goal of social and behavioral research is similar to that of clinical research — to establish a body of knowledge and to evaluate interventions — but the content and procedures often differ. Social and behavioral research involving human subjects focuses on individual and group behavior, mental processes, or social constructs and usually generates data by means of surveys, interviews, observations, studies of existing records, and experimental designs involving exposure to some type of stimulus or environmental intervention.

3. **Epidemiological Research.** Epidemiological research targets specific health outcomes, interventions, or disease states and attempts to reach conclusions about cost-effectiveness, efficacy, efficiency, interventions, or delivery of services to affected populations. Some epidemiological research is conducted through surveillance, monitoring, and reporting programs — such as those employed by the Centers for Disease Control and Prevention (CDC) —

whereas other epidemiological research may employ retrospective review of medical, public health, and/or other records. Because epidemiological research often involves aggregate examination of data, it may not always be necessary to obtain individually identifiable information. When this is the case, the PI should submit the research to the IRB to determine if it qualifies for an exemption or might be considered for an expedited review.

4. **Repository Research, Tissue Banking, and Databases.** Research utilizing stored data or materials (cells, tissues, fluids, and body parts) from individually identifiable living persons qualifies as human subject research, and requires IRB review. When data or materials are stored in a bank or repository for use in future research, the IRB should review a protocol detailing the repository's policies and procedures for obtaining, storing, and sharing its resources, for verifying informed consent provisions, and for protecting subjects' privacy and maintaining the confidentiality of data. The IRB may then determine the parameters under which the repository may share its data or materials with or without IRB review of individual research protocols. The VA has specific requirements for repository research.

5. **Quality Assurance/Quality Improvement Activities.** Quality assurance activities attempt to measure the effectiveness of programs or services. Such activities <u>may</u> constitute human subject research, and require IRB review, if they are designed or intended to contribute to generalizable knowledge. Quality assurance activities that are designed solely for internal program evaluation purposes, with no external application or generalization, will probably not require IRB review or will qualify for an exemption. In all cases, the IRB, not the individual Investigator, should determine when IRB review of such activities is required.

6. **Pilot Studies.** Pilot studies involving human subjects are considered human subject research and require IRB review.

7. **Human Genetic Research.** Genetic studies include but are not limited to: (a) pedigree studies (to discover the pattern of inheritance of a disease and to catalogue the range of symptoms involved); (b) positional cloning studies (to localize and identify specific genes); (c) DNA diagnostic studies (to develop techniques for determining the presence of specific DNA mutations); (d) gene transfer research (to develop treatments for genetic disease at the DNA level), (e) longitudinal studies to associate genetic conditions with health, health care, or outcomes, and (f) gene frequency studies. Unlike the risks presented by many biomedical research protocols considered by IRBs, the primary risks involved in the first three types of genetic research are risks of social and psychological harm, rather than risks of physical injury. Genetic studies that generate information about subjects' personal health risks may provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. For

many genetic research protocols, these psychosocial risks can be significant enough to warrant careful IRB review and discussion. Those genetic studies limited to the collection of family history information and blood drawing should not automatically be classified as "minimal risk" studies qualifying for expedited IRB review. Because this is a developing field, there are some issues for which no clear guidance can be given at this point, either because not enough is known about the risks presented by the research, or because no consensus on the appropriate resolution of the problem yet exists. OHRP representatives have advised that “third parties,” about whom identifiable and private information is collected in the course of research, are human subjects. Confidentiality is a major concern in determining if minimal risk is involved. IRB's can consider if informed consent from third parties can be waived in accordance with Section.116 and if so, document that in the IRB minutes. In most cases waiver of consent may be appropriate.

8. **Retrospective Chart Reviews.** Retrospective (medical) chart reviews are considered research when they attempt to answer a research question. These chart reviews include a “systematic investigation” that usually begins with a hypothesis. The process of “testing and evaluating” the data that is generated through the retrospective chart review is what defines this activity as research. Therefore, retrospective chart reviews that incorporate data collection and data analysis to answer a research question must undergo IRB review.

9. **Case Reports**. Case Reports are not considered research under most circumstances. Although identifiable information about a patient may be collected in preparing case reports, the intent of preparing case reports is usually related to patient care. A case report may contain information sometimes considered anecdotal in nature that discusses such areas as disease course, symptoms, response to treatment, unexpected events related to a disease process, or rare features of a disease process or response to therapy. In addition, many professional journals consider case reports to be educational in nature rather than research. Unless case reports are considered to be research, the following guidance should be applied:
    - Case reports do not have to be reviewed and approved by an Institutional Review Board or a Research and Development Committee because they are not considered research.
    - Educational activities are considered part of health care operations; therefore, a HIPAA authorization is not required if the information in the case report does not allow the reader to identify the person.
    - Case reports should contain only de-identified information or pictures that totally conceal the identity of the individual. Note: Consultation with a Privacy Officer may be necessary to confirm that the data and

pictures are de-identified. The Privacy Officer does have the authority to make this final determination.

- Written permission must be obtained from the individual if the data or the pictures are not de-identified.

There are circumstances in which case reports may be research involving human subjects. A determination whether a case report is considered research should be made by the Institutional Review Board (IRB) or a qualified individual or group of individuals. The following are circumstances when case reports may be considered research:

- The author of the case report develops a hypothesis and links other case reports to substantiate the hypotheses or to disprove the hypothesis. This activity may be similar to conducting a pilot study or a small epidemiological study. The results have become generalizable information.

- The intent is to develop generalizable information.

- It is part of a systematic effort to prove or disprove a point or some aspect of medicine or science.

B. The Principal Investigator (21 CFR 56.108(b), 312.64, and 312.66; VHA Handbook 1200.05, SOP RI 801

The Durham IRB recognizes one Principal Investigator (PI) for each project. The PI has ultimate responsibility for his/her research project and all official IRB correspondence is addressed to the PI. Co-Investigators communicate with the IRB through the PI.

As the individual responsible for the implementation of research, the principal Investigator bears direct responsibility for ensuring the protection of every research subject. This responsibility starts with protocol design, which must minimize risks to subjects while maximizing research benefits. The Investigator is also responsible for identifying a qualified clinician responsible for all study-related health-care decisions. In addition, the principal Investigator must ensure that all members of the research team always comply with the findings, determinations, and requirements of the IRB. The principal Investigator or designee is responsible for informing prospective subjects about all aspects of the study. The principal Investigator must also ensure the adequacy of both the informed consent document and the informed consent process, regardless of which members of the research team are authorized (by the Investigator) to actually obtain and document consent.

Principal Investigators are responsible for ensuring that (1) all human subject research that they conduct in the Durham VAHCS, as employees or agents of the VA, has received initial <u>prospective</u> review and approval; (2) continuing review and approval of the research has been accomplished within the time frame stipulated by the IRB); and

(3) the research is conducted at all times in compliance with all applicable regulatory requirements and the determinations of the IRB.

Initial reviews must be submitted to the IRB according to the deadline schedule provided on the VA Research Committee Meeting Dates form available through the Research Office. Protocol amendments/modifications should be promptly submitted to the IRB by the principal Investigator prior to implementation.
No changes in approved research or consent form may be initiated without prior IRB approval, except where necessary to eliminate apparent immediate hazards to subjects; and no research may be continued beyond the IRB-designated approval period (21 CFR 312.66).

Investigators must notify the IRB promptly of any local unanticipated serious adverse event related to the research or serious unanticipated problem related to the research, and any apparent serious or continuing non-compliance with applicable regulatory requirements or determinations of the IRB of which they become aware (21 CFR 56.108(b) and 312.64) and problems and/or events as described in SOP RR 403.

The IRB SOP 801 addresses the specific local procedures principal Investigators must follow to submit protocols to the IRB and conduct research. The necessary forms are available from the research office and on the research network.

C. Other Members of the Research Team
Every member of the research team is responsible for protecting human subjects. Co-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 adverse subject reactions or unanticipated problems, ensure the adequacy of the informed consent process, and take measures necessary to ensure adequate protection for subjects.

D. Sponsored Research
Research sponsored by commercial or non-commercial sponsors must be governed by a protocol. The contract shall explain the monitoring role to be taken by the sponsor, if any.

If the sponsor has a regulatory obligation to monitor the conduct of the study, the contract or funding agreement will include language that obligates the sponsor to promptly notify the PI and/or the IRB at Durham VAHCS of:

- Any information discovered by the sponsor representative that could:
    - Affect the safety of subjects;
    - Affect the willingness of subjects to continue participation;
    - Influence the conduct of the study; or
    - Alter the IRB’s approval to continue the study.

- Interim findings and post-study results that could affect the human subjects' protections associated with the study including information that may:
    - Affect the safety or medical care of current or former participants; or
    - Affect the willingness of participants to continue in the research;

- Acknowledge that post-study results would be reported in accordance with FDA regulations.

- The PI and/or the Durham VAHCS IRB after consultation with Sponsor will develop a plan for promptly disseminating study findings and results to Durham VAHCS study participants if applicable. The IRB will review any communication to participants before implementation.

Contracts should also address the Investigator's access to final study data and analysis for all sites and allow retention of a copy of the data generated at Durham VAHCS to document the research.

Sponsors may require confidentiality of sponsor-provided information and may request that the data generated by the study be treated as confidential information except for publications. The existence of the study agreement may not be confidential.

Multi-site studies should coordinate first publication of the entire study among the sponsor and sites within 12-24 months of the sponsor's lock of the study's database. Thereafter, each individual site should have the right to independently publish its own study data.

Submission of site proposed publications to a journal will be submitted to the IRB and R&D Committees for review.

E. Appeal of IRB Determinations [38 CFR 16.109(d)]

The IRB shall provide the PI with a written statement of its reasons for disapproving or requiring modifications in proposed research and must give the PI an opportunity to respond. The IRB must carefully and fairly evaluate the Investigator's response in reaching its final determination. The Investigator is encouraged to provide a written response to the IRB within sixty days of committee review. After sixty days the Investigator is sent a reminder notice.

F. Other Relationships within the VAHCS

The IRB requires projects involving Radiation therapy and biohazardous materials to be reviewed and approved by the Durham VAHCS Subcommittee on Research Safety (SRS). The SRS is a sub-committee of the R&D committee. Recommendations and committee minutes of the SRS are submitted to the R&D Committee for review. The SRS membership includes the Radiation Safety Officer. Approval by the SRS must be granted prior to final approval by R&D Committee before research can be started.

G. Regulatory Agencies

Statement of Authority and Purpose

The Durham VAHCS IRB and IRB records are subject to regulation and inspection by governmental regulatory agencies (e.g., FDA, GAO, and Office for Human Research Protections (OHRP), and the VA Offices of Research and Development (ORD) and Research Oversight (ORO). Copies of any reports or correspondence to and from such agencies concerning the VAHCS's IRB Committee must be provided by the IRB to the R&D Committee, which shall determine if any additional notifications are necessary. The Medical Center Director's signature is required on all formal reports submitted to such agencies.

H. Failure to Submit a Project for IRB Review

The implications of engaging in activities that qualify as research that is subject to IRB review without obtaining such review are significant. Results from such studies may not be published unless IRB approval had been obtained prior to collecting the data. To publish without approval violates Institutional policy. It is also against Institutional policy to use those data to satisfy thesis or dissertation requirements. If an Investigator begins a project and later finds that the data gathered could contribute to generalizable knowledge or that he or she may wish to publish or present the results of the activities, it is important that the Investigator submit a proposal to the IRB for review prior to release of such information. If the IRB does not approve the research, data collected cannot be used as part of a thesis or dissertation, and/or the results of the research cannot be published. Furthermore, FDA may reject such data if it is submitted in support of a marketing application.

Investigators who request approval to continue human subjects research that was not previously reviewed or to use data that was collected without IRB approval face the possibility that the IRB will administratively withdraw or request that the PI administratively withdraw his/her 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 subjects' 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 project.

GA 101: POLICIES AND PROCEDURES MAINTENANCE

1. Policy

Research at the Durham VAHCS must be conducted in an ethical manner (38 CFR 16.103(b)(1)). The institution is committed to the basic ethical principles that guide research involving human subjects as described in the Nuremberg Code, Declaration of Helsinki, and the Belmont Report. The three basic principles of the Belmont Report are central to the ethics of research involving human research and guide the IRB in assuring the rights and welfare of subjects are protected. These SOPs reflect the overarching commitment of the Durham VAHCS to provide protection for human subjects involved in research conducted under the direction of its employees, and staff.

As mandated by the DHHS, the Durham VAHCS has a written assurance with OHRP that it will comply with the requirements set forth in 45 CFR 46, the research conducted at this institution will be reviewed and approved by an IRB and will be subject to continuing review by the IRB.

The FWA outlines the principles and guidelines that govern the institution, employees and staff in the protection of the rights and welfare of the participants in the research conducted at or sponsored by the Durham VAHCS, regardless of the source of the funding.

Following federal regulations and guidance of ORD, ORO, OHRP, FDA, and local Durham VAHCS institutional policies ensures that the rights and welfare of the human subjects of such research will be overseen and protected in a uniform manner, regardless of changes in personnel. Written procedures must be in place to ensure the highest quality and integrity of the review and oversight of research involving human subjects and for the adequate documentation of such oversight.

Standard operating policies and procedures (SOPs) provide the framework for the ethical and scientifically sound conduct of human research.

1.1 Review, Revision, and Approval of Policies & Procedures

- Changes to regulations, federal guidelines, or research practice as well as the policies and procedures of Durham VAHCS may require a new SOP or a revision to a previously issued SOP.
- Policies will be reviewed by the appropriate institutional official(s) after 2 years or at intervals established by the ACOS/R&D.
- Approval of new or revised SOPs is required by the ACOS/R&D.
- Review and approval of SOPs will be documented in the minutes of the IRB and R&D.

1.2 SOP Dissemination and Training

- When new or revised SOPs are approved, they will be disseminated to all appropriate individuals & departments.
- Training will be provided to all members of the IRB, IRB staff, and the research community on any new or revised policy and/or procedure. This may occur by electronically placing revised documents on the shared research network, by town hall meetings, individual or group training, or other methods as appropriate.
- Each new IRB member or staff employee must review all applicable SOPs prior to undertaking any responsibilities of the IRB. Evidence of training must be documented and filed with the IRB Program Administer.

1.3 Forms

Forms are used to ensure that policies are integrated into the daily operations of research and review throughout the Durham VAHCS, and enable IRB staff to manage review, tracking, and notification functions consistently.

2. Scope

These policies and procedures apply to all IRB and research staff.

3. Responsibility

Medical Center Director is responsible for granting final approval (as appropriate) to new and revised IRB policies.

Research Compliance Officer has primary responsibility for auditing and reviewing research projects relative to requirements for the protection of human subjects.

ACOS/R&D is responsible for establishing and periodically reviewing and modifying (as appropriate) IRB standard operating policies and procedures.

The IRB, R&D Committee, AO/R&D, IRB Administrator, and/or HRPP Coordinator may revise research policies and procedures as necessary.

GA 102: RESEARCH REQUIRED TRAINING, EDUCATION, AND OTHER RESEARCH PERSONNEL DOCUMENTATION

1. Policy

Training of Investigators, research staff, IRB staff and members is critical if the IRB is to fulfill its mandate to protect the rights and welfare of research subjects in a consistent manner throughout Durham VAHCS research community.

Investigators, research staff, IRB members, IRB staff and others charged with responsibility for reviewing, approving, and overseeing human subject research should receive detailed training in the regulations, guidelines, ethics and policies applicable to human subjects' research. Responsibilities of researchers and their staff should are clearly communicated throughout these SOPs.

All members of the research team for a VA research study must be VA employees (paid, WOC, or IPA). The only individuals outside VA who do not need a VA appointment or VA-specific training are research consultants and those who perform a service for the research study in the course of their usual clinical duties.

1.1 Training

Management level staff and members of any IRB who are overseeing research on human subjects, as defined in 38 CFR 46.102 (f), 45 CFR 46.102 (f) and/or 21 CFR 56.102(e), that is managed, funded, or taking place at the Durham VAHCS will receive initial and ongoing training regarding the responsible review and oversight of research and these policies and accompanying procedures. Training must be completed before conducting human subject research. Training requirements also apply to staff of IRB-exempt studies or staff conducting human research with IRB-approved waiver of informed consent or waiver of documentation of informed consent.

ORD establishes the educational and training requirements for Investigators, research staff, IRB members and staff who review biomedical and behavioral research involving human subjects at this institution and who perform related administrative duties. Each individual involved in the conduct of human subjects' research (including the MCD, COS, R&D Committee members, and Research Pharmacist) is required to complete training in ethical principles concerning human subjects research. Initial and ongoing training is provided and documented by this institution through the Human Subjects Protection and Good Clinical Practice modules provided by ORD. Presently, these modules can be accessed on the Collaborative Institutional Training Initiatives (CITI) Program through the University of Miami. To meet the Federal-Wide Assurance

requirements the Network Director, Institutional Official and ACOS/R&D are also required to complete the OHRP *Human Subject Assurance Training Module*.

IRB members, Investigators, the research team, and research staff are required to update their research-related educational training every three years. The training must be completed within the third full calendar year after the previous training. Investigators who have not completed educational requirements will be in jeopardy of not having protocols approved in the future. Research staff not completing educational requirements will not be allowed to continue working on research projects until their training is complete.

IRB staff will receive initial and continuing training in all Standard Operating Policies and Procedures (SOPs).

IRB members and staff will be encouraged to attend workshops and other educational opportunities focused on IRB functions. PRIM&R meetings are recommended. The Durham VAHCS research service will support such activities to the extent possible and as appropriate to the responsibilities of members and staff.

The Durham VAHCS requires additional mandatory training; however, only research-related training is covered in this document. Durham VAHCS employees are responsible for completing all mandatory non-research training per Durham VAHCS policies.

Department of Defense (DoD) Research: Initial and continuing research ethics education is required for all personnel who conduct, review, approve, oversee, support or manage human research supported by the DoD or its Components. The type and extent of training depend upon the duties and responsibilities of the persons involved in the research.

- The PI consults the DoD Component, as appropriate, to identify education requirements.
- The PI is responsible for identifying specific educational or certification requirements of the sponsoring DoD Component and conveying those requirements to the IRB.
- When applicable, the PI, study personnel, and IRB members and staff complete DoD-specific research ethics training and the PI submits documentation of training completion to the IRB and to the DoD Component, as appropriate.

1.2 Scope of Practice

Each member of the Durham VAHCS research team (clinical or non-clinical) must have a research scope of practice (SOP) that defines the duties in which the person is

trained, qualified, and allowed to perform for research purposes. Research SOPs should be consistent with occupational categories. The scope of practice is required for all research personnel and must be signed by the individual, the individual's supervisor, each Principal Investigator (PI) that the individual works with, and the ACOS/R&D.

While individuals are accountable for their SOP, each PI is responsible for ensuring that individuals working on their study/studies have current and accurate SOPs. Individuals are responsible for keeping their SOP with their signature, their supervisor's signature, and all applicable PI signatures. Current scopes of practice documents with ACOS/R&D signature will be retained by the Research Office.

Note: The Research Pharmacist is not required to list every PI s/he works with (e.g., on a drug study) on his/her Research Scope of Practice.

1.2.1 Scope of Practice Updates/Revisions

- If an employee has a current Research SOP but is assigned to work with a PI that is not listed on the current Research SOP, the individual must complete a SOP PI Update Form and submit the form to the Research Office.
    - The new PI(s) must review the employee's Research SOP and sign and date the SOP PI Update Form to indicate that s/he agrees that the employee is capable to perform the assigned duties for those protocols in which s/he acts as the PI.
- If research duties or responsibilities change during the course of a year, the individual must submit a new SOP with the individual's signature, the supervisor's signature, and all applicable PI signatures for ACOS/R&D signature.

1.2.2 Competency Checklists

Vital Sign Competency Initial and Annual Review:

- If an employee collects vital signs from patients as part of his/her research duties and as indicated on the Research Scope of Practice, he/she must complete the Durham VAHCS Research Vital Sign Competency Initial and Annual Review Checklist. This checklist list must be completed initially and annually so long as his/her research duties include the collection patient vital signs. The competency must be signed and dated by the research staff member and preceptor and submitted to the Research Office. While individuals are accountable for maintaining this competency checklist, it will be retained by the Research Office. For individuals meeting waiver status, the competency checklist should only be completed and submitted initially (ONE-TIME) to indicate waiver status has been

met. Licensed Independent Practitioners (e.g., MD), including Residents, are exempt from completing the Vital Sign Competency Checklist. The checklist must be completed and submitted to the research office whenever there is a change in waiver or exempt status.

Blood Collection Competency Checklist:

- If an employee performs venipuncture (blood draws) as part of his/her research duties and as indicated on the Research Scope of Practice, he/she must complete the Blood Collection Competency Checklist. This checklist list must be completed initially and annually so long as his/her research duties include blood draws for research purposes. The competency must be signed and dated by the research staff member and preceptor and submitted to the Research Office. While individuals are accountable for maintaining this competency checklist, it will be retained by the Research Office. For individuals meeting waiver status, the competency checklist should only be completed and submitted initially (ONE-TIME) to indicate waiver status has been met. Licensed Independent Practitioners (e.g., MD), including Residents, are exempt from completing the Blood Collection Competency Checklist. The checklist must be completed and submitted to the research office whenever there is a change in waiver or exempt status. If applicable, the current date of Blood Collection Competency must be listed on the Sub-committee for Research Safety (SRS) form Research Using Human Blood, Tissue, or Cell Lines at initial and continuing review.

1.3 Staff Listing

The Staff Listing provides a list of all personnel who conduct any part of the research endeavor. The Staff Listing must be submitted at initial and continuing review and must include the names of all individuals either involved in the conduct of the study or who make decision regarding study procedures.

- Identify on the form whether the staff are physically housed at the Durham VAHCS or elsewhere.
- Any staff that conducts any portion of research at the Durham VAHCS must be covered by some type of VA appointment (i.e., VA-paid, WOC, IPA, or contract).
- Individuals who are not conducting the research but are associated with the study should be listed as a Consultant, regardless of VA appointment status.
- Durham VAHCS is not responsible for tracking research-required training for Consultants who do not have Durham VAHCS appointments.

- If a researcher is employed at another VA institution, that individual should be listed on the Staff Listing, but their home VA is responsible for tracking educational requirements.
- For individuals with a Durham VAHCS appointment who are involved in the conduct of the study, the Staff Listing also provides the completion dates of CITI GCP training. The presence of a research Scope of Practice
- is also documented on the Staff Listing.
- The PI should keep all Staff Listings and training records of staff members with their specific protocol files.
- The IRB will also keep all Staff Listings in the IRB's research file, and will maintain an electronic copy of the Scope of Practice.
- Addition or removal of Durham VAHCS appointees should be documented on the Staff Listing and submitted as personnel changes occur; however, changes in consultants or off-site VA personnel may be submitted at continuing review.

Note: The Durham VAHCS IRB does not require the Research Pharmacist to be listed on the study Staff Listing; however, the Research Pharmacist can be listed if the Sponsor requests that s/he be listed.

1.4 Credentialing and Privileging

The employee must have all required licenses, registrations, or certifications to perform a given procedure, intervention, or other activity in the research setting and practice only within the scope allowed by such licenses, registrations, or certifications.
All VA research Investigators and staff (clinical and non-clinical) conducting human research (exempt or non-exempt) must be credentialed and privileged (if applicable) as required by current local, VA, VHA (see VHA Handbook 1100.19), and ORD requirements. Research Investigators and staff (including volunteers) may only perform those activities in a research study for which they have the relevant credentials and privileges.

1.5 Documentation

Training and continuing education shall be documented and maintained in an educational database created by the Research office and added to the records of the IRB as described in these policies and procedures. All documentation of training for Investigators and research staff is maintained on file in the Research office.

All Staff Listings are maintained in individual protocol files in the Research Office. Current Scope of Practice documents with ACOS/R&D signature are retained by the Research Office.

2. Scope

These policies and procedures apply to all Investigators, and staff, IRB members, R&D members, executive leadership (as described above), and research staff.

3. Responsibility

ACOS/R&D is responsible through the MCD for establishing, conducting and/or supervising all relevant training programs for Investigators, research team members, IRB members and staff.

IRB Chairperson (or designee) is responsible for guiding the development of IRB member training programs, in collaboration with the ACOS/R&D, AO/R&D, Program Administrator and Research Compliance Officer.

GA 103: MANAGEMENT OF IRB PERSONNEL

1. Policy

IRB staff provides consistency, expertise, and administrative support to the IRB and R&D committees, and serve as a daily link between the IRB and the research community. Thus, the IRB staff is the most vital component in the effective operation of Durham VAHCS's human subjects' protection program. Therefore, the highest level of professionalism and integrity on the part of IRB staff is expected.

1.1 Job Descriptions and Performance Evaluations

Members of the IRB staff should have a description of the responsibilities expected of their positions. The performance of IRB staff will be reviewed according to current Durham VAHCS policy.

1.2 Staff Positions

Staffing levels and function allocation will be determined according to Durham VAHCS policy, management assessment of support requirements, and budget constraints.

1.3 Hiring and Terminating IRB Staff

The Human Resource policies of Durham VAHCS determine the policies for recruiting and hiring staff.

1.4 Delegation of Authority or Responsibility

Delegation of specific functions, authorities, or responsibilities by the ACOS/R&D to a staff member must be documented in writing.

1.5 Documentation

The policies of Durham VAHCS's Department of Human Resource Management determine the means of identifying, documenting and retaining formal staff interactions (such as performance reviews, termination procedures).

2. Scope

These policies and procedures apply to all IRB staff.

3. Responsibility

The Medical Center Director (MCD) is responsible for ensuring adequate administrative personnel, equipment, and space for the local research office. The MCD, along with the Associate Chief of Staff/Research & Development (ACOS/R&D) and Administrative

Officer/Research & Development (AO/R&D), is responsible for establishing personnel requirements and for hiring and evaluating the ongoing performance of the Program Administrator and for guiding the Program Administrator in establishing personnel requirements for other IRB staff.

AO/R&D and Program Administrator are responsible for establishing personnel requirements and for hiring and evaluating the ongoing performance of IRB staff.

IRB Chairperson (or designee) is encouraged to provide input on the ongoing performance of the IRB Program Administrator and IRB staff to the ACOS/R&D and AO/R&D.

The IRB Program Administrator oversees the day-to-day operations of the Research office staff to ensure consistency and provide support to the Investigators, IRB and R&D committee.

GA 104: CONFLICT OF INTEREST

1. Policy

In the environment of research, openness and honesty are indicators of integrity and responsibility, characteristics that promote quality research and can only strengthen the research process. Therefore, conflicts of interest should be eliminated when possible and effectively managed and disclosed when they cannot be eliminated. It is the policy of the Durham VAHCS that any individual responsible for the design, conduct, review, or reporting of a research project disclose significant personal financial interests related to the project. When it is determined that such an interest might reasonably appear to be directly and significantly affected by the project, the Durham VAHCS will take steps to either eliminate or manage the conflict.

All Investigators are required to disclose personal, professional and/or financial conflict of interest by completing the Conflict of Interest Agreement form when submitting protocols for initial IRB approval and continuing review, and when new financial interests related to the active project are acquired. IRB consultants are required to disclose personal, professional and/or financial conflict of interest by completing a Conflict of Interest Survey when reviewing protocols at the request of the IRB. IRB members and IRB consultants are required to disclose potential or actual conflict of interest at the beginning of, or during each IRB meeting. The IRB chairperson identifies IRB member conflict of interest at the beginning and during each meeting. IRB members are required to recuse themselves during discussion and deliberations of protocols posing a conflict of interest and will not be counted in the vote or towards the quorum.

1.1 ***Definition of a COI***

The term conflict of interest refers to situations in which financial arrangements, or other personal considerations may directly or significantly affect or have the appearance of exerting inappropriate influence on the design, review, conduct, results or reporting of research activities or findings.

A conflict of interest can also be a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of the study) is potentially unduly influenced by a secondary interest (such as a financial gain).

The VHA's current Research Conflict of Interest Statement outlines conditions in which a possible conflict of interest may exist.

Concerns related to conflicts of interest have increased as the relationships of Investigators with private corporations, pharmaceutical companies, and outside institutions have become more complex. These concerns are based on the potential

effects the conflicts may have on the actual or perceived quality of the research and the treatment of research participants.

The main conflict of interest statute in the federal criminal code, 18 U.S.C. §208, prohibits all VA employees (full time, part time, WOC, and IPA) from participating personally and substantially, as part of their official duties, in any particular matter, including research, that directly and predictably affects their own financial interests or any financial interests imputed to them. Financial interests that are imputed to a VA employee include the financial interest of a spouse; minor child; general partner; an organization in which the VA employee serves as an officer, director, trustee, general partner, or employee; or an organization with which the VA employee is negotiating or has an arrangement for prospective employment. Imputed financial interests are treated as if they were the VA employee's own financial interest for purposes of this prohibition.

In addition to the disclosures required in *Research Financial Conflict of Interest Statement* form (required with protocol submission), all VA employees are subject to the criminal conflict of interest statutes at Title 18, U.S.C. Chapter 11, and the Executive Branch Standards of Conduct at Title 5 CFR Part 2635. Violation of these provisions may be sanctioned by civil and criminal penalties, as well as employment-related discipline such as removal or suspension.

1.2 Disclosure and Documentation of Financial Interest and COI

No regular IRB member, alternate IRB member, or consultant may participate in the initial, continuing review, expedited review of any research project, review of unanticipated problems involving risks to subjects or others, or review of regulatory noncompliance in which the member has a conflict of interest. Individuals involved in the design, conduct, or reporting of the research protocol are considered to have a conflict of interest. Individuals who have immediate family members (defined as spouse and/or dependent children) involved in the design, conduct, or reporting of the research are considered to have a conflict of interest.

It is the responsibility of each voting member or alternate member of the IRB to disclose any COI in a study submitted to the IRB and recuse him or herself from deliberations and voting.

The procedures for recusal of IRB members, including the Chairperson, from deliberating/voting on all protocols for which there is a potential or actual conflict of interest are detailed in SOP FO 303.

It is the responsibility of each Investigator to disclose whether any significant financial interest exists (this includes sub-investigators and spouse and/or dependent child of the Investigator) by completing a Research Financial COI Statement form when submitting

protocols. Criteria for financial interest are documented on this form. The requirement that an Investigator report a significant financial interest does not imply the existence of an actual or potential conflict of interest. The existence of a conflict of interest is determined by the IRB when evaluating each COI form. If a COI is determined to exist the IRB may require additional information or steps to manage, reduce, or eliminate the conflict.

A Research Financial COI Statement must be filed at initial and continuing review and when new financial interest related to the active project is acquired.

Consistent with 21 CFR Part 54, disclosable financial arrangements of a clinical Investigator (includes sub-investigator, Investigator spouse and dependent child) that a sponsor is required to submit to the FDA include:

1. Compensation made to the Investigator in which the value of compensation could be affected by study outcome.
2. A proprietary interest in the tested product, including, but not limited to a patent, trademark, copyright or licensing agreement.
3. Any equity interest in the sponsor of a covered study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices.
4. Any equity interest in a publicly held company that exceeds $50,000 in value. These must be disclosed only for covered studies that are ongoing on or after February 2, 1999. This applies to interest held during the time the clinical Investigator is carrying out the study and for 1 year following completion of the study.
5. Significant payments of other sorts, which are payments that have a cumulative monetary value of $25,000 or more made by the sponsor of a covered study to the Investigator or the Investigators' institution to support activities of the Investigator exclusive of costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainer for ongoing consultation or honoraria) during the time the clinical Investigator is carrying out the study and for 1 year following completion of the study.

It is the responsibility of the each clinical Investigator and sub-investigator (the term Investigator includes the spouse and dependent child of the Investigator) who is directly involved in the treatment or evaluation of research subjects in a FDA-regulated research study to disclose these arrangements to the IRB.

1.3 Employees

Institutional staff whose job status or compensation is affected by research that is reviewed by the IRB must recuse themselves from any meeting during the time when such a protocol is reviewed.

1.4 Education and Training in COI

Investigators, IRB members and staff are required annually by the Durham VAHCS to participate in Compliance Business and Integrity education and training activities related to financial conflict of interest issues.

1.5 Review of COI Forms

The IRB Chairperson (or designee) will review all COI forms. If a real or potential conflict of interest is determined to exist, the real or potential conflict of interest will be forwarded to the IRB for review at a convened meeting.

The IRB Chair (or designee) is responsible for evaluating each COI form at initial and subsequent reviews (revised/updated forms) to determine whether any real or potential conflicts of interests (financial, role [Investigator/patient relationships], and/or institutional) would appear to directly or significantly impact each proposed research study.

Direct impact occurs when the study results will be directly relevant to the development, manufacturing, or improvement of the products or services of the organization in which the Investigator has a financial interest, or when the organization is a proposed subcontractor or participant in the study. A significant impact on the financial interest is one that will materially affect the value of the organization, its earnings, or the sales of its products, or the organization is a proposed subcontractor or participant in the project. The IRB may determine that there is no reasonable basis on which to conclude that a research study could directly and significantly affect the financial interest and the financial interest is not likely to affect the design, conduct, or reporting of the study.
All COI forms, even those with a negative statement, must be reviewed by the IRB (chair or designee). In the event that the IRB determines that a study might have a direct or significant impact on the financial interest and the financial interest could affect the design, conduct or reporting of the study, the disclosure will be forwarded to the R&D committee for review prior to final study approval. The Investigator will be asked to document how the COI is managed and/or the IRB may impose conditions or restrictions to manage the conflict of interest. The IRB will take appropriate action within the scope of its authority to approve, disapprove, or require modifications to seek approval when reviewing conflicts of interest. The IRB will document its decision of whether COI exist or not on the IRB Reviewer Checklist. The decision, conditions or restrictions and actions of the IRB imposed on the Investigator will be documented in the minutes of the IRB and maintained in the IRB protocol files.

Examples of these conditions or restrictions may include but are not limited to:

1. Public disclosure (disclosure in the informed consent document to human subject participants) of significant financial interests;
2. Monitoring of the research by independent reviewers;

3. Modification of the research plan;
4. Disqualification from participation in all or a portion of the research study;
5. Divesture of significant financial interests; or
6. Severance of relationships that create actual or potential conflicts.

In order to ensure protection of the participants, the IRB will consider the following when reviewing a conflict of interest regardless of funding source or regulatory oversight:

1. Risks and anticipated benefits to the subjects;
2. Whether other actions are necessary to minimize risks to subjects;
3. The selection of subjects;
4. The possibility of coercion or undue influence;
5. The kind, amount, and level of detail of information to be provided to research subjects regarding the source of funding, funding arrangements, and the financial interests of parties involved in the research;
6. Provisions for monitoring the safety of the subjects;
7. Whether methods used for management of financial interest of parties involved in the research adequately protect the rights and welfare of the subjects;
8. The impact of the financial conflicts of interest on the subject, the subject's willingness to participate in the research after the disclosure of the conflict, and the impact on the research and the research results.

1.6 Organizational Conflict of Interest

Actual or apparent Organizational Conflict of Interest can occur at the Durham VAHCS (Institution) when the Institution stands to gain financially from patents or inventions disclosed by VA staff. If the inventor's VA time, or VA resources are utilized in conceiving the invention, then the local VA stands to benefit financially.

VA Employees are required to disclose Inventions or patents to the VA Office of Research and Development's Technology Transfer Office using the "Certification for Reporting Inventions" and "Outline for Report of Inventions and Certification Made by Employees of the Department of Veterans Affairs" forms. The "Certification for Reporting Inventions" form requires signatures of the inventor, the inventor's supervisor and the ACOS/R&D. VA renders a decision based upon the disclosure information and that decision as to whether VA assert rights to the technology is communicated in writing to the inventor via the ACOS/R&D. If the VA asserts rights to the invention, then the local institution could stand to benefit financially.

The ACOS/R&D is an ex-officio member of the IRB. If human subjects are involved, or if the study has had prior IRB review, the ACOS/R&D communicates and submits the results of disclosures of invention to the IRB with all relevant study information. The IRB will then follow the same procedure as above for managing a potential or real conflict of interest.

Institutional conflict of interest may result from but are not limited to institutional pressures for:

1. A speedy approval;
2. A desire to reverse a negative IRB decision;
3. The protection of the Durham VAHCS at the expense of protecting the participants;
4. A desire to protect Investigators at the expense of the participants.

In an effort to manage institutional conflicts of interest, IRB and R&D members with a conflict of interest are required to verbally disclose their conflict prior to the review of a research study and recuse themselves from the deliberations and voting of such research. The Medical Center Director, COS, ACOS/R&D, and AO/R&D will serve as nonvoting members of the R&D committee. The IRB must be independent from the influence of the institution. If the IRB disapproves a research study, the institution is not allowed to reverse the decision. Members of the IRB who feel they are being unduly influenced are to report the episode to the Medical Center Director and the ACOS/R&D.

1.7 Undue Influence of IRB Members and Staff

The IRB is an autonomous body, and any attempts to unduly influence a member of the board will not be tolerated. IRB members and staff who believe that an Investigator, sponsor, member of the study team or any other person has attempted to exert undue influence to coerce the IRB member or staff will provide the IRB Chair with a Report of Contact detailing name(s), date(s) and pertinent information. The IRB Chair will forward this information to the Medical Center Director and the ACOS/R&D, who will initiate a fact-finding. In no case will the IRB consider the protocol in question until the fact-finding has been completed. If there is a question of undue influence involving either of these individuals, the Report of Contact will be provided to the Integrated Ethics Officer, who will refer it to the appropriate administrator. The ACOS/R&D will present his/her findings to the IRB. The IRB has full authority to take corrective action as deemed necessary. Corrective actions may include, but are not limited to, project suspension, Investigator suspension, or more frequent continuing reviews. The ACOS/R&D will also submit the results of the fact-finding to the R&D Committee and Chief of Staff for consideration of appropriate administrative action.

The conditions or restrictions to manage, reduce, or eliminate the conflict of interest must be completed, strategies developed, or procedures instituted prior to R&D committee approval.

1.8 Failure to Disclose a COI

Failure to disclose a COI or update an existing conflict with any condition or restriction imposed by the IRB will result in disciplinary actions. The Medical Center Director has

the authority to determine when COI exists as defined by VA policy and to impose and enforce disciplinary action in the event that COI is not disclosed. In addition, if the failure of the Investigator to comply with the conflict of interest policy of the Durham VAHCS has biased the design, conduct, or reporting of PHS-funded research, the Durham VAHCS must promptly notify the PHS Awarding Component of the corrective action taken or to be taken. The PHS Awarding Component will consider the situation and, as necessary, take appropriate action or refer the matter to the Durham VAHCS for further action. The PHS Awarding Component may also review on site all records pertinent to compliance of this regulation, require further corrective action, or suspend funding until the matter is resolved. The failure to disclose a COI is considered serious noncompliance with VA policy and is reportable to ORO.

2. Scope

These policies and procedures apply to all Investigators, IRB members and IRB consultants, of the Durham VAHCS. These policies not only apply to research projects sponsored by the U.S. Public Health Service, which includes the National Institutes of Health as published in 42 CFR Part 50 and 45 CFR Part 94, but is expanded to include other extramural sponsors.

This policy applies to all research conducted at the Durham VAHCS regardless of funding source or regulatory oversight and is consistent with DHHS regulations found at 42 CFR Part 50 and 45 CFR Part 94 and FDA regulations found at 21 CFR Part 54.

3. Responsibility

The Medical Center Director is responsible for articulating and enforcing the conflict of interest policy (COI) at the Durham VAHCS.

IRB is responsible for monitoring the COI status and disclosures of Investigators and IRB members.

IRB Chairperson (or designee) is responsible for reviewing all COI forms and identifying IRB committee COI disclosures before beginning (and during) every IRB meeting. After reviewing the COI form, if the IRB Chairperson (or designee) determines that a real or potential Conflict of Interest exists, the conflict of interest will be forwarded for review at a convened IRB meeting.

Program Administrator, Program Specialist and Program Support for research are responsible for documenting COI discussions in IRB meeting minutes.

GA 105: SIGNATORY AUTHORITY

1. Policy

The Institutional Official (IO) is the Medical Center Director. The IO is the VA official responsible for ensuring that the HRPP at the facility has the resources and support necessary to comply with all federal regulations and guidelines that govern human subjects' research. The IO is legally authorized to represent the institution, is the signatory official for all Assurances, and assumes the obligations of the institution's Assurance. The IO is the point of contact for correspondence addressing human subjects' research with OHRP, FDA, and VA Central Office.

The R&D and IRB Chairperson(s) are authorized to sign any and all documents in connection with the review and approval of research projects involving the use of humans as subjects, which have been reviewed and approved pursuant to Durham VAHCS policies and procedures. This policy applies to all staff of the IRB. In all cases individuals must sign their own name and no other and indicate their title under their signature.

Individuals signing documents in connection with the review and approval of research protocols involving human subjects must be officially authorized to do so. Authorization to sign documents not described in this policy may be made in writing to the ACOS/R&D or designee.

1.1 Authorization for Signatory Authority

Authorization to sign documents not described in this policy may be made in writing to the ACOS/R&D.

1.2 Results of Reviews, Actions and Decisions

The results of reviews and actions taken by the IRB, either by the convened IRB or by expedited review, that grant or may appear to grant Investigators with initial or continuing approval of research, training or educational projects involving human subjects, may be signed by R&D and IRB Chairpersons (or designee). IRB primary reviewers are authorized to sign documents indicating fulfillment of recommended IRB actions required in order for the Investigator to seek final approval.

1.3 Routine Internal Correspondence

Any action, letters, memos or emails between the IRB, and/or members of the staff of the Durham VAHCS that provides information concerning the review of research protocols by the IRB or staff which do not imply or appear to imply approval of this activity, may be signed by IRB Program Administrator or RCO or other designated staff members.

1.4 Routine Correspondence with the IRB

Any memorandums, request for amendments, modifications, notifications of adverse events or any information from the Investigator to the IRB concerning a research protocol may be executed by a research coordinator or research assistant but must bear the signature of the Investigator.

1.5 Correspondence with External Agencies

Any letters, memos or emails sent to agencies of the federal government, funding agencies (whether private or public) or their agents will be signed by the Medical Center Director. Some documents may bear the signature of both the MCD and ACOS/R&D.

1.6 Decisions Made by Chairperson

Any letters, memos or email sent representing the decision or opinions of the R&D and IRB, as long as such correspondence does not imply review and approval of research projects, will be signed by the Chairperson or designee.

2. Scope

These policies and procedures apply to all IRB staff.

3. Responsibility

ACOS/R&D is responsible for establishing the overall procedure for delegating signatory authority.

IRB Program Administrator is responsible for implementing and controlling signatory authority delegations.

IRB Chairperson, members and staff are responsible for adhering to institutional signatory authority policies.

OR 201: COMPOSITION OF THE IRB

1. Policy

The IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. Each IRB should also be able to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

The IRB will have at least five regular, voting members with varied backgrounds to promote complete and adequate review of research activities commonly conducted at the Durham VAHCS for which it reviews research. The IRB members are sufficiently qualified to review the research through their experience, expertise, and diversity, including consideration of race, gender, cultural backgrounds, and sensitivity to community issues and/or attitudes. Qualified persons from multiple professions and of both sexes shall be considered for membership. IRB membership shall not consist entirely of men or of women.

Research staff including, but not limited to the ACOS/R&D, AO/R&D, and IRB administrative staff, may not serve as voting members of IRB; but may serve as ex officio, non-voting members.

The institution will ensure that a diverse membership is appointed to the IRB, within the scope of available expertise needed to conduct its functions.

1.1 Membership Selection Criteria

The members of the IRB shall be sufficiently qualified through experience and expertise, for reviewing research proposals in terms of regulations, applicable law and standards of professional conduct and practice, and institutional commitments. Therefore, the IRB shall include persons knowledgeable in these areas.

The membership shall be diverse, so selection shall include consideration of race, gender, cultural backgrounds, clinical experience, healthcare experience and sensitivity to such issues as community attitudes to assess the research submitted for review.

There shall be at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. There shall be one member who has no affiliation with this institution, either self or family member. The nonaffiliated voting member must be given a VA without compensation (WOC) appointment.

The chairperson shall be an employee of the Durham VAHCS, appointed by the Medical Center Director for a term of three years and may be re-appointed indefinitely.

For FDA-regulated research, there shall be at least one member who is a licensed physician.

For ED-regulated research funded by the National Institute on Disability and Rehabilitation Research, if the research purposefully requires inclusion of children with disabilities or individuals with mental disabilities as research participants, the IRB must include at least one person primarily concerned with the welfare of those participants.

IRB members are obligated to protect research subjects and ensure that the integrity of the review process is not compromised by competing business interests. Thus, individuals who are responsible for business development cannot serve as IRB members or carry out the day-to-day operations of the review process.

1.2 Composition of the Board

Regular members: The backgrounds of the regular members shall be varied in order to promote complete and adequate reviews of the types of research activities commonly reviewed by the IRB. Regular members must include:

A. Nonaffiliated member(s): The nonaffiliated member(s), who can be either scientific or nonscientific reviewers, should be knowledgeable about the local community (otherwise known as the Veteran population) and be willing to discuss issues and research from that perspective.

   The nonaffiliated voting member must be given a VA WOC appointment if the nonaffiliated voting member is going to be performing the duties and fulfilling the responsibilities of an IRB voting member. The nonaffiliated voting member still would be considered “not otherwise nonaffiliated” with VA if there is documentation that the only reason for the WOC appointment relates to liability coverage for the member’s IRB responsibilities.

   Consideration should be given to recruiting individuals who speak for the veteran population from which the Durham VAHCS will draw its research subjects. The nonaffiliated member(s) should not be vulnerable to intimidation by the professionals on the IRB, and their services should be fully utilized by the IRB.

   Veterans whose only relationship with VA is receiving care at a VA facility or receiving benefits from the Veterans Benefits Administration (and have never been employed by VA) are not considered to be affiliated for the purpose of being an IRB member. Individuals who perform occasional volunteer activities without a WOC appointment are not considered affiliated. However, those who hold a WOC appointment for volunteer activities other than IRB service are considered to be affiliated. Note:

Former employees who have retired from VA and who are receiving VA retirement benefits are considered affiliated.

Employees of institutions that have formal academic affiliation agreements with VA, and employees of VA nonprofit research and education foundation are considered to be affiliated with VA.

B. Scientific members: The IRBs may consist of physicians, nurses, pharmacists, and Ph.D. level physical or biological scientists. Such members satisfy the requirement for at least one scientist. Social workers, statisticians, and clinical allied health professionals are also considered to be scientists. The IRB will identify an expert who is competent in an area of research interest to use as a consultant to assist in the review of research beyond the expertise of the committee members. However, when FDA regulated products are reviewed, the convened meeting must include a licensed physician member; therefore, at least one (1) member of the IRB must be a physician licensed in any state.

C. Nonscientific member: The intent of the requirement for diversity of disciplines is to include members whose main concerns are not in scientific areas. Therefore, nonscientific members are individuals whose education, work, or interests are not solely in medical or scientific areas.

D. Consultants or Representatives of special groups of subjects: When certain types of research are reviewed, members or consultants who are knowledgeable about the concerns of certain groups, vulnerable populations, have competence in special areas, or scientific knowledge of the research context will be required. The IRB Committee will include at least one member with expertise in the area of the cognitively impaired population when reviewing studies with this population or studies in which the subjects may become cognitively impaired throughout the course of the research. An individual with specialized knowledge will be consulted and requested to review and/or provide input in initial and/or continuing review for the IRB. This individual will be invited as a non-voting guest to the convened IRB meeting and will not count towards the quorum. The IRB may authorize the Chair or designee to seek consultants. The IRB may wish to respect the Investigator's intellectual property; therefore, prior to assigning a consultant, Investigators will be asked if there is anyone they would not like to review their study. Consultants will be subject to Conflict of Interest requirements applicable to IRB members.

An individual IRB member may:

- Request the Chair to appoint a consultant whenever the member determines the assigned protocol requires expertise in

a special area beyond his/her ability to provide an adequate review.

- Recommend a person whom (s)he contacted for information related to the research to serve as a consultant.

The IRB may:

- Decide during the review discussion if a consultant is needed to assist in the review;
- Authorize the Chair (or designee) to seek consultants subject to their approval.
- Approve the appointment of a consultant to the IRB.

The Consultant:

- Certifies in writing that (s)he has no conflicting interest.
- Receives all documents of the protocol submitted to the IRB for review and after consultation returns the documents.
- Presents opinions on the protocol either orally at the time of the convened meeting or by written summary.
- If present at the meeting, departs the meeting before the final IRB deliberation and vote on the protocol on which (s)he gave input.

E. Chairpersons: The individual IRB Chairpersons should hold a paid VA appointment and be fully capable of managing the IRB and the matters brought before it with fairness and impartiality.

F. Alternate members: Regular members may suggest Alternate member(s) to substitute in their absence. An Alternate member will be appointed in the same manner as a Regular member. Alternate members will have qualifications comparable to those of the Regular member and serve in the same capacity as the member for whom they substitute. Alternate members may attend IRB meetings but will only vote when serving as a substitute for the regular member.

G. Ex-officio members: Include but are not limited to the ACOS/R&D, AO/R&D, Information Security Officer, and Privacy Officer. Ex-officio members may not be included in the quorum count and may not vote with the IRB. Ex-officio members may provide guidance on local, VA and federal regulations.

H. Research Compliance Officer (RCO): The RCO(s) act as a consultant to the IRB, but does not serve as a voting or nonvoting member. The Durham

VAHCS IRB and R&D Committee have requested that RCOs attend IRB and R&D meetings.

2. Scope

These policies and procedures apply to the membership of the IRB.

3. Responsibility

Medical Center Director is responsible for ensuring the IRB has adequate resources to identify and recruit qualified potential members and for appointing the members to their respective terms.

ACOS/R&D (or AO/R&D) is responsible for recruiting and installing new IRB members.

OR 202: MANAGEMENT OF THE IRB

1. Policy

The management of the membership of the IRBs and oversight of member appointments, IRB related activities, communications, and other administrative details are the responsibility of the ACOS/R&D (or AO/R&D).

IRB function is evaluated by the R&D Committee, ACOS/R&D, COS and Director on a continuous basis, and at least annually. The R&D reviews the actions of the IRB monthly through the committee minutes. The AO/R&D is a non-voting member of the IRB and evaluates its functions on a continuous basis.

1.1 Term

Members will serve terms not to exceed three years on staggered appointments but appointments may be extended as deemed necessary by the Medical Center Director. Reappointment for additional terms may occur, by mutual agreement of the member and Medical Center Director.

1.2 Appointments

The Medical Center Director in consultation with the ACOS/R&D and AO/R&D has the authority to appoint members to the IRB. Appointments are done in writing. Members will be solicited from the Durham VAHCS and communities in and surrounding Durham county. Names of potential new IRB voting members must be submitted to the Medical Center Director in writing.

1.3 Evaluations

The IRB Chair annually evaluates the performance of voting members of the IRB using the “Institutional Review Board Committee Member Evaluation” form. The review is done in advance of the R&D Committee Annual Quality Assurance Review. Within 30 days after completing the IRB Performance Review, the IRB Chair meets with each voting member, discusses the evaluation, solicits feedback and offers suggestions for improvements, if warranted.

The IRB Chair is a VA employee. The IRB Chair’s performance appraisal includes elements (identified below) specifically addressing the Chair’s performance of IRB duties.

A. Ensures that research conducted meets the standards and expectations for protection of human subjects, biosafety/biosecurity, and research information security that are defined by VA policy. Deficiencies identified in any of these areas have either been remedied by the end of the performance period, or there is a VISN-approved plan to remedy within 6 months.

B. Specifically, provide administrative support for the Research Program by serving as Chairperson for the Medical Center institutional review board (IRB) for human subjects' research.

The Chair's supervisor seeks input from the ACOS for Research regarding the Chair's performance of IRB duties. The Chair's supervisor incorporates these comments into the performance appraisal prior to presenting and discussing with the Chair.

1.4 Resignations and Removals

A member may resign before the conclusion of his/her term. The vacancy will be filled as quickly as possible. The Medical Center Director is responsible for suspending or terminating IRB membership for any individuals who are not fulfilling their member responsibilities or obligations.

1.5 Compensation

IRB Chairperson(s) may receive protected time to conduct IRB business. Participation by Durham VAHCS staff is considered a component of their job responsibilities as established by their supervisors. Community members shall receive compensation from Durham VAHCS's research non-profit organization, the Institute for Medical Research (IMR).

1.6 Liability Insurance

Regular and alternate members are protected from liability under the Tort Claims Act as part of their IRB membership in their capacity as agents of the Durham VAHCS. Community members are covered under the Tort Claims Act as part of their membership in their capacity as WOC employees.

2. Scope

This policies and procedures apply to the IRB membership.

3. Responsibility

The Medical Center Director in consultation with ACOS/R&D (or designee) and R&D Committee is responsible for the oversight of the IRB and must assure that IRB members are appropriately knowledgeable to review and approve research in accordance with the ethical standards and all applicable regulations.

IRB Program Administrator is responsible for day-to-day management of the activities of the IRB members.

IRB Chairperson is responsible for management of the activities of the IRB members relevant to meeting conduct and review of research.

OR 203: DUTIES OF IRB MEMBERS

1. Policy

Each IRB member's primary duty is the protection of the rights and welfare of the individual human beings who are serving as the subjects (veterans and non-veterans) of that research. The IRB member must understand that he or she is not serving on the IRB to expedite the approval of research, but to be a gatekeeper between the Investigator and the research subjects. In order to fulfill their duties, IRB members are expected to be versed in regulations governing human subjects' protection, biomedical and behavioral research ethics, and the policies of Durham VAHCS germane to human subjects' protection.

1.1 Duty to the Durham VAHCS

The IRB is appointed as an Institutional sub-committee of the R&D. As such, the IRB members serve Durham VAHCS as a whole, rather than a particular department. Therefore, members must not allow their own interest or that of their department to supersede their duty to protect the rights and welfare of research subjects.

1.2 Term of Duty

The Durham VAHCS IRB Chairperson(s) must be appointed by the Medical Center Director for a term of 3 years and may be re-appointed indefinitely. Durham VAHCS IRB members (regular and alternate) must be appointed by the Medical Center Director for a period of 3 years and may be re-appointed indefinitely. During their appointments on the IRB, IRB members and Chairpersons are expected to fulfill certain duties. These duties will be described prior to appointment and each IRB member is expected to fully understand the duties of IRB members prior to accepting appointment as an IRB member. New members receive a letter from the Medical Center Director documenting his/her appointment and time commitment.

1.3 Specific Duties

1.3.1 Regular Members

- Nonaffiliated member(s): Nonaffiliated members are expected to provide input regarding their knowledge about the local community and veteran population (where applicable), and be willing to discuss issues and research from that perspective.
- Non-scientific members: Nonscientific members are expected to provide input on areas germane to their knowledge, expertise and experience, professional and otherwise. Non-scientific members should advise the IRB if additional expertise in a non-scientific area is required to assess if the protocol adequately protects the rights and welfare of subjects.

- Scientific members: Scientific members are expected to contribute to the evaluation of a study on its scientific and statistical merits and standards of practice. These members should also be able to advise the IRB if additional expertise in a non-scientific area is required to assess if the protocol adequately protects the rights and welfare of subjects.
- Chairperson: In addition to the above responsibilities (germane to the member's capacity), the Chairperson leads IRB meetings. The Chairperson performs or delegates to an appropriate voting IRB member expedited review when appropriate. They are empowered to temporarily suspend the conduct of a clinical trial deemed to place individuals at unacceptable risk, pending IRB review. The Chairperson is also empowered, pending IRB review, to suspend the conduct of a study if he/she determines that an Investigator is not following the IRB's requirements.

The Chairperson may appoint a Co-chairperson to assist or act on behalf of the Chairperson in particular IRB matters and at IRB meetings, either as a general procedure, or on a case-by-case basis. The Chairperson also may delegate any of his/her responsibilities as appropriate to other qualified individual(s). The Chairperson may designate the expedited or exempt review procedure to a member who is qualified by experience and training. The qualified designee must be a voting member with experience and knowledge of the content of the subject matter to be reviewed. The individual must be knowledgeable in the processes, procedures, and regulations relative to reviewing and approving research expeditiously. An experienced reviewer is an IRB voting member who has completed human subjects protection and Good Clinical Practice training and served as primary reviewer on research protocols for 12 or more IRB meetings, or has completed at least one full term as an R&D member.
The task of making the IRB a respected part of the institutional community will fall primarily on the shoulders of these individuals. The IRB must be perceived to be fair and impartial, immune from pressure either by the institution's administration, the Investigators whose protocols are brought before it, or other professional and nonprofessional sources.

1.3.2 Primary Reviewers

In addition to the duties described in section 1.3.1, each regular member will be expected to act as a Primary Reviewer for assigned studies at convened meetings. The IRB Program Administrator along with the IRB Chairperson assigns studies consistent with the reviewer's area of expertise and content of the protocol. Two Primary Reviewers are assigned to all amendment/modifications and initial reviews not meeting exempt criteria. The Primary Reviewers presents their findings resulting from review of the application materials and provides an assessment of the soundness and safety of the protocol and recommends specific actions to the IRB, and uses the IRB Initial Review checklist to document their findings. They lead the IRB discussion of the study.

Primary Reviewers may be required to perform an assessment through the study of relevant literature, have discussions with colleagues, contact the principal Investigator, and review additional material requested by the IRB for the purpose of study approval. Primary Reviewers may notify the Chair and IRB Program Administrator prior to or at the scheduled IRB if s/he cannot adequately evaluate the assigned protocol. The Chair can decide whether to review the protocol, assign the protocol to another member, invite a consultant, defer it to another meeting, or invite the PI to present the research during the scheduled meeting.

The Chairperson (or designee) acts as the Primary Reviewer for all Continuing Reviews, Adverse Events, Protocol Deviations, and Compliance Reviews. Some Adverse Events and Protocol Deviations may also be assigned to a Primary Reviewer.

1.3.3 Ex-Officio Members

Ex-Officio members are non-voting members of the committee by virtue of their positions within the local facility. These members include but are not limited to the ACOS/R&D, AO/R&D, Information Security Officer, and Privacy Officer. These members may offer expert advice on the conduct of the meeting and issues of human subjects' protection and Good Clinical Practice but are never included in the quorum count and are never voting members.

2. Scope

These policies and procedures apply to all IRB Members.

3. Responsibility

The ACOS/R&D or AO/R&D and IRB Program Administrator identify potential members, and discuss the requirements and responsibilities of IRB members with each member prior to appointment.

IRB Program Administrator is responsible for clearly articulating all IRB members' duties to potential and current IRB members.

IRB Members are responsible for fulfilling their duties as specified.

FO 301: RESEARCH SUBMISSION REQUIREMENTS

1. Policy

IRB members often rely solely on the documentation submitted by Investigators for initial and continuing review. Therefore this material must provide IRB members with enough information about a study to assess if it adequately meets the IRB's criteria for approval. All submissions must include the principal Investigator's signature where requested.

A submitted protocol will be scheduled for IRB review when staff has determined that the information and materials submitted present an adequate description of the proposed research.

1.1 Submission Requirements for Initial Review

As there may be difference in biomedical and behavioral research, some documents may or may not be required based on study characteristics. Submit documents that are applicable to the proposed research.

- Protocol
- Durham VAHCS-specific protocol if the research is conducted at multiple sites
- Request to Review/Investigator Overview
- Page 18 (for new Investigators)
- Abstract or Study Summary
- Questionnaires and/or assessment instruments
- Proposed informed consent document or waiver
- Proposed subject instructions/information sheets
- Checklist for Reviewing Privacy, Confidentiality, and Information Security in Research completed and approved by the ISO and PO
- Any other supporting material, such as examples of recruitment advertising, etc.
- Waiver of Informed Consent to Screen and Recruit (this form is combined with the waiver of HIPAA authorization to screen and recruit)
- Health Insurance Portability and Accountability Act (HIPAA) documents
    - HIPAA Authorization
    - HIPAA Waiver of Authorization (Combined with Waiver of Informed Consent)
        - Required to screen, recruit, and/or conduct
        - Required when requesting waiver or alteration of consent
- HIPAA Declaration of Limited Data Set and Data Use Agreement form (if applicable)
- Conflict of Interest Survey for all Investigators

- Staff Listing Form (of individuals involved in the proposed research project)
- Human Subjects Training and Good Clinical Practice training documentation for Investigator/co-Investigator and all research staff (if not on file in Research office)
- Scope of Practice for all research staff (if not already on file in the Research office)
- Research Vital Sign Competency Checklist for staff collecting vital signs for research (if not already on file in the Research office and if applicable)
- Blood Collection Competency Checklist for staff preforming blood draws for research (if not already on file in the Research office and if applicable)
- VA Form 10-0398 Research Protocol Safety Survey ((Appendix G) Safety Submission if the research involves biological, chemical, physical, or radiation hazards)
- Standard Operating Procedures for Using Human Blood or Tissue
- Recombinant DNA and/or Viral Vector form
- Training to pack and/or ship biological samples
- Copy of the Merit Review or grant with budget (required for federal granting agencies)
- FDA Form 1572
- IND approval number/IND letter
- Form 10-9012
- Investigator Brochure or device specifications
- Package Insert if FDA approved
- Investigation Device Exemption (IDE) approval
- Documentation that the study has been reviewed and approved by the IRB charged with oversight of research at a participating investigative site (e.g., the VHA Central IRB)
- Case report form(s)
- Additional information if research is funded by the Department of Defense or the Department of Education
- Data Management and Access Plan (DMAP) that describes the conditions and mechanisms the publications and final data sets resulting from research will be shared with the public.

1.2 Submission Requirements for Continuing Review

1.2.1 Changes in Study Status

During the approval period, Investigators must submit documentation to inform the IRB about changes in the status of the study including, but not necessarily limited to:

- Deviations from the protocol, that pose a risk to subjects safety, rights or welfare
- Reports of serious, unexpected adverse events and unanticipated problems, both of which are related to the research

- Information security and privacy incidents which require immediate reporting (see RR403)
- For IND / IDE studies, reports of serious or unexpected adverse events that occur during the approval period as required by FDA regulation
- Changes to the status of Principal or Co-Investigators
- Changes in the status of the research study personnel

1.2.2 Progress Report and/or Request to Renew IRB Approval

Thirty to Sixty (30-60) days prior to IRB approval expiration date and at least 14 business days prior to the scheduled IRB meeting, Investigators requesting renewal of an approved research project must submit:

1. A completed Request for Continued Approval of Human Use form
2. A written Progress Report, which includes:
    a. Brief summary of the research methodology and procedures;
    b. Number of subjects entered and withdrawn (including the reason for withdrawal) for the review period and since the inception of the research project;
    c. The gender and minority status of those entered into the protocol;
    d. Number of subjects considered as members of specific vulnerable populations;
    e. A copy of the proposal and all approved amendments;
    f. Information that may impact on the risk benefit ratio such as AEs, unanticipated problems, and complaints regarding the research;
    g. Research findings to date, if available;
    h. Summary of the DSMB or DMC meetings (if applicable) or findings based on information collected by the data and safety monitoring plan submitted in the initial proposal;
    i. An assurance that all SAEs and UAEs have been reported as required;
    j. New scientific findings in the literature, or other relevant findings, that may impact on the research.
3. Informed Consent Document, as applicable
    - the IRB approved and stamped consent form and
    - a copy of an unstamped form
4. VA Form 10-0398 Research Protocol Safety Survey Annual Certification (Appendix G Certification)
5. HIPAA Authorization Form
6. Monitoring Reports (from Sponsors)
7. A summary of all adverse events and protocol deviations that occurred during the review period.
8. A list of all SAEs that occurred during the review period, including the PI's determination on whether the event was unanticipated and/or related to research.

1.3 Action Taken If Documentation is Not Adequate or Additional Information is Required

The Research Office staff determines that the submitted documents are not adequate; in addition, the IRB may identify the package incomplete for review. Investigators may be required to submit additional information, or their presence may be required to answer questions or explain the details of the study. No submission deemed as incomplete by Research Office staff will be reviewed by the IRB. Incomplete submissions will be referred back to the Principal Investigator for completion.

2. Scope

These policies and procedures apply to all research submitted to the IRB regardless of whether the review is expedited or by convened meeting.

3. Responsibility

IRB Program Administrator is responsible for maintaining current research submission requirements for interested Investigators and for preliminary triage of non-routine submissions.

IRB Program Administrator is responsible for preparing member review materials and reviewing submission elements.

IRB Program Administrator, Program Specialist, Program Support Specialist are responsible for submission receipt, tracking and acknowledgements.

FO 302: RESEARCH EXEMPT FROM IRB REVIEW

1. Policy

Research activities in which the only involvement of human subjects will be in one or more specific categories, which are listed in 38 CFR 16.101(b) (see section 1.1 of this policy), may be exempt from continued IRB review. Note: Common Rule exemptions at 38 CFR 16.101 (b) may not be applied to FDA-regulated research (see 21 CFR 56.104 for exemptions applied to FDA-regulated research). Determination of exemption must be based on regulatory and institutional criteria and documented.

The IRB's first responsibility is to determine whether or not the proposed project constitutes a research study. If the project does not constitute research, the IRB has no responsibilities for review or approval beyond the determination that the project does not constitute research.

No study can be initiated until the IRB has determined that the study does not constitute human subjects research, is exempt from IRB approval requirements, or has satisfied all requirements for approval.

1.1 Exempt Research Activities (non-FDA regulated)

Research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from IRB review (38 CFR 16.101(b)(1)):

1. Research (non-FDA regulated) conducted in established or commonly accepted educational settings, involving normal educational practices, such as:
   i. Research on regular and special education instructional strategies,
   ii. Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research (non-FDA regulated) involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, <u>unless</u> (38 CFR 16.101(b)(2)):
   i. Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
   ii. Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, reputation or loss of insurability.

3. Research (non-FDA regulated) involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under category #2 above, if (38 CFR 16.101(b)(3)):
   i. The human subjects are elected or appointed public officials or candidates for public office; or
   ii. Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. Research (non-FDA regulated) involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the Investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects (38 CFR 16.101(b)(4)):
5. Research and demonstration projects (non-FDA regulated) which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine (38 CFR 16.101(b)(5)):
   i. Public benefit or service programs;
   ii. Procedures for obtaining benefits or services under those programs;
   iii. Possible changes in or alternatives to those programs or procedures; or
   iv. Possible changes in methods or levels of payment for benefits or services under those programs.
   v. The program under study delivers a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act).
   vi. The research is conducted pursuant to specific federal statutory authority.
   vii. The proposed research is under no statutory requirement to be reviewed by the IRB.
   viii. The research does not involve significant physical invasions or intrusions upon the privacy of participants.
   ix. The exemption has authorization or concurrence by the funding agency.
   x. The research is not subject to FDA regulation.

6. Taste and food quality evaluation and consumer acceptance studies (38 CFR 16.101(b)(6)):

   i. If wholesome foods without additives are consumed, or

   ii. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

1.2 Exempt Research Activities (FDA-regulated)

The following categories of FDA-regulated clinical investigations are exempt from the requirements for IRB review (21 CFR 56.104):

1. Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981; and the research is not “research” involving “human subjects” as defined by DHHS regulations.
2. Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date; the research is not “research” involving “human subjects” as defined by DHHS regulations.
3. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use the test article at the institution is subject to IRB review and the use is not “research” involving “human subjects” as defined by DHHS regulations.
4. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

1.3 Granting Exemptions

Investigators must submit the proposed research along with any relevant materials (e.g., questionnaire, survey, or test instrument to be given to participants) and/or the request for exemption to the IRB. Applicable grant applications, request for waiver of

HIPAA authorization or a declaration of de-identified data form must also accompany the submission when applicable.

The IRB Chair, or an experienced IRB voting member designated by the Chair, must review all requests for exemption in a timely manner and make a decision based on 38 CFR 16.101. When reviewing exempt research the following criteria will be used to determine that participants are protected:

a. The research involves no more than minimal risk to participants.
b. Selection of participants is equitable.
c. If there is no recording of identifiable information, and there are adequate provisions to maintain the confidentiality of the data.
d. If there are interactions with participants, there will be a process that will disclose such information as:
    i. That the activity involves research.
    ii. A description of the procedures.
    iii. That participation is voluntary.
    iv. Name and contact information for the Investigator.
e. There are adequate provisions to maintain the privacy interest of participants.

The decision must be communicated in writing to the Investigator and the IRB documenting the specific category justifying the exemption.

1.4 Documentation of Exempt Status

The IRB's determination of exemption must be signed by the IRB voting member who reviewed the research and made the determination that the research was exempt, or denied the exemption and include the specific categories justifying the exemption from IRB review or, if the request is denied, include the reason for denial.

Projects that are exempt from IRB review must be reviewed by the R&D Committee prior to initiation and then they must be included in its annual review of research projects.

1.5 Determination of Human Subject Research

When Durham VAHCS engages in research (per OHRP Guidance: Engagement of Institutions in Human Subjects Research, October 16, 2008), the IRB is authorized to make the following determinations for research involving humans:

1. Whether or not the proposed research satisfies the definition of human subjects research; and

2. Whether or not the proposed research is exempt from federal human research subjects protection regulations.

Only the IRB can make an authoritative determination as to whether an activity is human subjects' research. No Investigator is authorized to determine that his or her human subjects' research is exempt. Determinations of whether research involving humans constitutes research in human subjects under, or is exempt from, federal human subjects' protection regulations may be delegated by the IRB Chairperson(s) to an experienced IRB member knowledgeable about this area of federal regulation. All determinations must be made in accordance with applicable federal regulations and guidance. Only federal exemptions may be recognized by the IRB. Durham VAHCS does not consider research involving only coded private information or coded human biological specimens to involve human subjects as described by OHRP guidance if the following conditions are met:

1. The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and

2. The Investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
   a. The key to decipher the code is destroyed before the research begins;
   b. The Investigators and the holder of the key enter into an agreement prohibiting the release of the key to the Investigators under any circumstance, until the individuals are deceased;
   c. There are IRB-approved written polices and operating procedures for a repository or data management center that prohibits the release of the key to the Investigators under any circumstances, until the individuals are deceased; or
   d. There are other legal requirements prohibiting the release of the key to the Investigators, until the individuals are deceased.

For research involving humans that is determined to be exempt from, or not human subjects research under, federal human research subjects protection regulations, the IRB is authorized to review any proposed or implemented change(s) to the research to determine whether it alters the previously assigned status of the research. For research that is determined to be exempt or not human subjects' research, the IRB is authorized to review the research to determine if the research meets Durham VAHCS's ethical standards. Durham VAHCS has adopted the principles of the Belmont Report as its ethical standard for research. Ethical review may be accomplished by expedited review procedures or a convened IRB meeting.

2. Scope

These policies and procedures apply to Investigator claims for exemption from IRB review.

3. Responsibility

IRB Program Administrator or HRPP Coordinator is responsible for evaluating submissions that claim exemption from IRB review.

IRB Chairperson (or designee) is responsible for providing consultation in the review of claims of exemption.

IRB Chairperson (or designee) is responsible for approving an exemption request or routing to full committee.

FO 303: IRB MEETING ADMINISTRATION

1. POLICY

Except when an expedited review procedure is used, the IRB will conduct any business including, but not limited to, voting on actions and reviewing and approving proposed research at convened meetings at which a quorum is present. The IRB will meet monthly, the second Thursday of each month, or at some other frequency determined by the IRB Chairperson and the IRB Program Administrator.

Facility Directors, their administrative staff, Chiefs of Staff, and other local leadership may observe IRB meetings, but may not be voting or ex officio, non-voting members of the VA facility's IRB of record.

1.1 Quorum

A quorum is defined as a majority of the voting members as listed on the IRB membership. The Chair calls the meeting to order when a quorum is established, suspends business and cannot vote when the quorum is lost, and resumes business when the quorum is re-established.

A quorum consists of regular and/or their alternate members and must include at least one member whose primary concerns are in non-scientific areas.

When FDA-regulated research is reviewed, there shall be one member who is a physician.

For ED-regulated research funded by the National Institute on Disability and Rehabilitation Research, if the research purposefully requires inclusion of children with disabilities or individuals with mental disabilities as research participants, the IRB must include at least one person primarily concerned with the welfare of those participants.

An alternate member may attend in the place of an absent regular member in order to meet the quorum requirements outlined above. However, the alternate must receive review materials in advance and have sufficient time to review materials prior to the IRB meeting.

A special consultant(s) will be non-voting and will not be used to establish a quorum.

A member with a conflict of interest cannot contribute to a quorum, be present for the discussion of the issue for which they are conflicted (except to answer questions from the committee), or be present for the vote on the issue.

If the IRB reviews research that involves categories of human subjects vulnerable to coercion or undue influence, one or more individuals who are knowledgeable about or experienced in working with such subjects are present.

1.2 Primary Reviewers

Prior to the meeting, the IRB Program Administrator (in consultation with the Chairperson(s) will designate two primary reviewers for each research proposal. The primary reviewer's duties are described in SOP OR 203.

1.3 Meeting Materials Sent Prior to IRB Meetings

All IRB members will be sent study documentation required for review sufficiently in advance of the meeting to allow time for adequate review. These include:

1.3.1 Agenda

A meeting agenda will be prepared by the IRB Program Administrator or designee and distributed, along with reviewer materials, to IRB members one week (7 days) prior to each meeting. A copy of the agenda and attached materials will be maintained on file in the research office until the IRB meeting has concluded.

The IRB Chairperson will remind members to declare any potential COI they may have with research that is about to be reviewed at the outset of each meeting. The Chairperson will ask for a declaration of such conflict and this will be incorporated in the minutes of the meeting. The IRB minutes will also specifically reflect such recusals as they occur during meetings. Recused members leave the room and are not part of the deliberations or vote. They may be asked to provide information regarding the study.

1.3.2 Reviewer materials

A. All IRB Members (at a minimum)
   - A completed Request to Review Proposal/Project, Investigator Overview, Abstract or Summary and conflict of interest statement
   - Proposed informed consent document(s) and/or script as appropriate
   - Surveys, questionnaires, advertisements, physician letters

B. Primary Reviewers
   - Full Investigator’s or Sponsor’s protocol
   - A completed Request to Review Proposal/Project, Investigator Overview, and conflict of interest statement
   - Proposed informed consent document(s) and/or script as appropriate
   - Copies of surveys, questionnaires, or videotapes
   - Copies of letters of assurance or cooperation with research sites

- Investigator Brochure (if one exists) or device specifications
- Advertising intended to be seen or heard by potential subjects, including email solicitations and physician letters
- Grant Application: The primary reviewers will review the grant application (e.g. DHHS approved protocols), if any, to ensure that the research described in the IRB proposal is consistent with the grant application. The grant application does not need to be reviewed by every IRB member. A copy of the grant application or proposal should be retained by the Research Office and made available to any IRB member who may wish to review it. The IRB may require the Investigator(s) to: (i) summarize, and cross-reference to the application, specific information contained in the grant application; (ii) identify any IRB-approved protocols that describe the proposed research; and (iii) either certify that the application or proposal is consistent with any corresponding IRB protocol(s) or submit protocol amendments to reconcile any discrepancies.
- IRB Review of NIH-Approved (DHHS-approved) Informed Consent Documents
- NIH-Supported Multi-center Clinical Trials: If available, for NIH-supported multi-center clinical trials the IRB must receive and review a copy of the NIH-approved sample informed consent document and the full NIH-approved Investigator's protocol as a condition for review and approval of the local informed consent document. Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the Investigator, approved by the IRB, and reflected in the IRB minutes.

1.4 Minutes

The IRB Program Administrator or designee will record the deliberations and take minutes of each meeting using the Management of IRB (MIRB) Program. Draft minutes of IRB meetings must be written and available for review within 3 weeks of the meeting date. Once approved by the voting members at a subsequent IRB meeting, the minutes must be signed by the IRB Chair, or a qualified voting member of the IRB designated by the Chair. The final minutes cannot be altered by anyone, including other authorities or committees (e.g., the VA facility Director, RCO, Privacy Officer or ISO, or the R&D Committee). Final minutes will be provided to the R&D Committee for review and approval; then the final IRB minutes approved by the R&D Committee will be sent to the Medical Center Director and Chief of Staff.

The IRB Program Administrator will maintain copies of the minutes and pertinent materials on file (see SOP FO 305). Minutes of IRB meetings must be in sufficient detail to document:

A. Attendance: Attendance at the meetings includes those members or alternate members who participated through videoconference or teleconference, and documentation that those who attended through videoconferencing or teleconferencing received all relevant material prior to the meeting and were able to actively participate in all discussions.

B. Quorum: There must be the presence of a quorum for each vote, including the presence of one voting member whose primary concern is in a non-scientific area. If quorum is lost, the IRB cannot take votes until the quorum is restored. ***NOTE:*** *This quorum, including the presence of one voting member whose primary concern is in a non-scientific area, could be indicated in the minutes by tracking attendance. It does not have to be indicated with each vote.*

C. Alternate Members: If applicable, document the presence of alternate members attending the meeting and for whom they are substituting.

D. IRB Actions: Document actions taken by the IRB. This includes documenting approval of research contingent on specific minor conditions by the Chairperson.

E. Vote: Document the vote on these actions including the number of voting members voting for, against, and abstaining (see SOP RR 406). Members recused due to a conflict of interest will be specifically named in the minutes. Members who leave the room due to a conflict of interest will not be counted towards the quorum. Comments made at the IRB meeting will not be attributed to individual members. Identification of individuals' votes will not be recorded.

F. IRB Member Conflict of Interest: When an IRB member has a potential, actual, or perceived conflict of interest relative to the proposal under consideration, the member will recuse themselves from the discussion, except to provide information requested by the IRB (38 CFR 16.107(e). The member with the conflict of interest must not be present during the vote or during any related IRB discussion except to answer questions. The member with the conflict of interest cannot be counted toward quorum. The minutes will document that the IRB member was not present during the deliberations or vote on the proposal, and that the quorum was maintained. ***NOTE:*** *"Not present" means that an IRB member must leave the room or, if participating in the meeting by conference call or videoconference, must have terminated the connection.*

G. IRB Determinations and Justifications:

(1) Document determinations made by the convened IRB when those determinations are required by applicable VA and other Federal requirements.

(2) Document protocol-specific findings justifying those IRB determinations for:

(a) Waiver or alteration of the informed consent process in accordance with 38 CFR 16.116(c) and (d)), or (38 CFR 16.117(c);

(b) Research involving pregnant women;

(c) Research involving prisoners; and

(d) Research involving children.

NOTE: *The minutes must specifically document that the IRB determined that all criteria for waiver or alteration of the informed consent process were met.*

(3) If an IRB uses an expedited review process, these determinations and protocol-specific findings justifying those IRB determinations must be documented in either the IRB protocol file or the minutes.

H. Risk Device Determinations: Document rationale for significant risk/non significant risk device determinations.

I. Vulnerable Populations: Document any review of additional safeguards to protect vulnerable populations if entered as study subjects and findings related to the use of surrogate consent.

J. Subjects Susceptible to Coercion or Undue Influence: Document that safeguards are adequate to protect the rights and welfare of subjects who are likely to be susceptible to coercion or undue influences.

K. Risk and Rationale: Document the IRB's determination of the level of risk (e.g., whether or not the research constitutes minimal risk) and the rationale for the IRB's determination of the level of risk.

L. Informed Consent Requirements: Document the IRB's determination that all appropriate elements were included in the informed consent form, and are

included in the informed consent process. In studies using an informed consent form, the form must include appropriate blocks for signatures and dates.

M. Frequency of Continuing Review: Document the IRB's determination of the frequency of continuing review of each study.

N. Approval Period: For initial and continuing review, the approval period.

O. Changes or Disapproval: Document the basis for requiring changes in or disapproving research.

P. Controverted Issues: Provide a summary of the discussion of controverted issues and their resolution.

Q. Significant New Findings: Provide statements of significant new findings.

R. Non-Veteran Subjects: Provide a summary of the justification for including non-Veterans as subjects.

S. Real Social Security Numbers: Provide a summary of the discussion when real Social Security Numbers (SSNs), scrambled SSNs, or the last four digits of SSNs will be used in the study. The summary needs to include the security measures that are in place to protect the SSN instances embedded in the study. ***NOTE:*** *This does not apply if the only use of SSNs is on the informed consent form or the HIPAA authorization as required by VHA Handbook 1907.01).*

1.5 Telephone/Video Use

1.5.1 Convened meeting using Telephone Conference (speakerphone)

Should a member not be able to be physically present during a convened meeting, but is available by telephone, the meeting can be convened using a teleconference or speakerphone. The member who is not physically present will be connected to the rest of the members via telephone conference call or speakerphone. In this manner, all members will be able to discuss the protocol even though one or more members are not physically present. Members participating by such telephone conference call will receive all pertinent material prior to the meeting and may vote, provided they have had an opportunity to review all the material the other members have reviewed. "Telephone polling" (where members are contacted individually) will not be accepted as a conference call. The minutes will reflect those members who participate via teleconference.

1.5.2 Meetings Conducted Via Video Conference Calls

On occasion, meetings may be convened via a video conference call (one or more members). A quorum (as defined above) must participate for the video conference call meeting to be convened. To allow for appropriate discussion to take place, all members must be connected simultaneously for a conference call to take place. Members participating by videoconference call will receive all pertinent material prior to the meeting and may vote, provided they have had an opportunity to review all the material the other members have reviewed. Members not present at the convened meeting, nor participating in the conference call may not vote on an issue discussed during a convened meeting (no voting by proxy). The minutes will reflect those members who participate via videoconference.

1.6 Voting

Members of the IRB vote upon the recommendations made by the primary reviewers according to the criteria for approval (see SOP RR 402 and 404). A majority of members present must vote in favor of an action for that category of action to be accepted by the IRB. Only regular and alternate members acting in place of absent regular members may vote. Members also will determine level of risk, and the frequency of review for each protocol.

IRB members cannot participate in the meeting discussions or voting by email.

2. Scope

These policies and procedures apply to all research submitted to the IRB.

3. Responsibility

IRB Program Administrator is responsible for IRB meeting procedural conduct and documentation.

IRB Chairperson (or designee) is responsible for IRB meeting review conduct and leadership.

FO 304: ADMINISTRATIVE REVIEW AND DISTRIBUTION OF MATERIALS

1. Policy

The efficiency and effectiveness of the IRB is supported by administrative procedures that ensure that IRB members not only have adequate time for thorough assessment of each proposed study, but that the documentation they receive is complete and clear enough to allow for an adequate assessment of study design, procedures, and conditions.

1.1 Exemptions

The IRB Program Administrator will review Claims for Exemption submitted by Investigators in consultation with the IRB Chairperson. Such Claims of Exemption will be logged, filed, and distributed to the IRB Chairperson or designee for review as described in SOP FO 302. If the Chairperson determines and documents that the proposed research meets exemption criteria, the research will be submitted to the R&D committee for review and approval. If the claim does not meet exemption criteria, the project will be submitted to the convened IRB meeting or the Investigator may be asked to make revisions to meet exemption. Investigators will be notified in writing of the outcome of the claim for exemption.

1.2 Incomplete Submissions

Incomplete applications will not be accepted for review until the Investigator has provided all necessary materials as determined by the IRB Chairperson, or IRB Program Administrator, or designee. The IRB Program Administrator will notify the submitting Investigator to obtain any outstanding documentation or additional information before the application is scheduled for review.

1.3 Scheduling for Review

Complete applications that appear to meet qualifications for expedited review will be submitted to the Chairperson or designee. If a submission meets expedited review requirements, the review will be performed as described in SOP RR 401 (Expedited Review). All other applications will be placed on the agenda for the earliest meeting possible for review by the full IRB as described in SOP FO 303 (IRB Meeting Administration).

1.4 Distribution to Members Prior to IRB Meetings

Copies of application materials described in SOP FO 301 (Research Submission Requirements) will be distributed to all IRB members, generally at least seven (7) days prior to the meeting. Each regular member of the IRB, and any alternate members attending the meeting in place of a regular member, will receive a copy of the initial

application material as described in SOP FO 303. Consultants will only receive copies of material that pertain to their requested input.

The originals of submission materials will be retained in the Research Office and available for the IRB meeting.

1.5 Confidentiality

All material received by the IRB will be considered confidential and will be distributed only to meeting participants (regular members, alternate members and special consultants) for the purpose of review. All application materials will be stored in an IRB study file with access limited to the R&D members, IRB members, and staff. All other access to the IRB study file will be approved by the IRB Program Administrator as deemed appropriate.

2. Scope

These policies and procedures apply to all research submitted to the IRB.

3. Responsibility

Investigators seeking IRB prospective approval will submit materials as described in SOP FO 301 by IRB submission deadline.

IRB Program Administrator (or equivalent) is responsible for conducting appropriate assessment of submissions for triage purposes.

IRB Program Administrator or designee is responsible for providing complete review material packets to IRB members and other relevant parties.

IRB Chairperson (or designee) is responsible for supporting and assisting the IRB Program Administrator in submission triage activities.

FO305: DOCUMENTATION AND DOCUMENT MANAGEMENT

1. Policy

The IRB's files must be maintained in a manner that contains a complete history of all IRB actions related to review and approval of a protocol, including continuing reviews, amendments and adverse event reports. All records regarding a submitted study (regardless of whether it is approved) must be retained in an appropriate manner as required by regulatory requirements and/or institutional policy.

The Research office shall prepare and maintain adequate documentation of IRB activities, to include copies of all research proposals reviewed (approved and unapproved), accompanying scientific evaluations (if any), approved sample consent documents, progress reports, reports of injuries, minutes and agendas of IRB meetings. These records will be retained and destroyed per current VHA Records Control Schedule for research records.
Records must be accessible to the R&D Committee and for inspection and copying by authorized representatives of the Sponsor, funding department or agency, regulatory agencies and institutional auditors at reasonable times and in a reasonable manner. Required documents must be submitted to the appropriate funding entity as required.

IRB records are the property and responsibility of the local research office.

1.1 Investigator Notifications

1.1.1 Initial Submission

The Investigator will be notified in writing of the IRB's decision as soon as possible after the meeting. If the approval is pending upon receipt and review of requested materials or responses from the Investigator or Sponsor, the IRB must receive the response within 90 days of the date of notification; however, this period may be extended if needed.

1.1.2 Renewals and Revisions

Investigators will be notified in writing as soon as possible as to action taken by the IRB for any continuing reviews or revisions.

1.1.3 Notification of Final Approval

Investigators will be notified in writing of the final approval. IRB approval of a study means the IRB has determined that the research has satisfied all relevant approval criteria and may be conducted at the Durham VAHCS within the constraints set forth by the IRB and by other applicable local, VA, and other Federal requirements.

Final written notification will be provided to Investigators after R&D Committee review and approval and ACOS signature. All SRS Committee recommendations must be approved before the R&D Committee can review the protocol. The IRB-approved consent form will be dated with the period of approval and submitted to the Investigator with the final approval letter. Standard conditions for continued approval include, but are not necessarily limited to:

- Informed consent is obtained and documented per SOP IC 701-703.
- The IRB is notified of SAEs, unanticipated problems, changes to the protocol, and protocol deviations as described in SOP RR 403.
- Continuing Review reports are submitted per SOP RR 404.
- Documentation of FDA approval prior to study initiation (if applicable).

1.1.4 Disapproval

Correspondence will provide the reason(s) for disapproval and instructions to the Investigator for resubmission or appeal of this decision.

1.2 Document Retention

The Research Office must retain required records, including the Investigator's research records, as required by the National Archives and Records Administration and VHA's Records Control Schedule (RCS 10-1). Records include 1) applications (regardless of whether it is approved), 2) records for all approved protocols without participant enrollment, and 3) records for all applications that are approved and the research initiated. After the record retention period has ended, the records will be destroyed per current VHA Records Control Schedule for research records. Electronic records from closed studies and prior investigators will be maintained in file locations that allows for access to the data. If the prior investigator and co-investigator(s) are no longer at the DVAHCS, the Research Office will be responsible for maintaining electronic research records.

Records will be organized (reverse chronological order) to reconstruct a complete history of all IRB actions related to the review and approval of the protocol. IRB documentation will clearly reflect what the IRB actually approved. IRB records for initial and continuing reviews by an expedited procedure will include the specific permissible category, description of the review, any action taken by the reviewer, and any findings required by federal regulations. For exemption determinations or non-human use designation the IRB records will include citation of the specific category justifying the exemption or the basis for the non-human use designation. IRB records for each protocol's initial and continuing review will include the frequency of the next continuing

review (not to exceed 1 year) and contain a copy of the final approved informed consent document.

1.2.1 Study-Related Documents

The IRB records consist of all copies of all: research proposals reviewed; scientific evaluations, if any, that accompany the protocols; approved informed consent forms; progress reports submitted by Investigators; and reports of injuries to subjects (38 CFR 16.115(a)(1)). The IRB protocol file must contain copies of all items reviewed including, but not limited to, <u>all versions</u> of:

a. Research protocols.
b. Investigator's Brochures, if any.
c. Recruitment materials, if any.
d. Scientific evaluations, if any, that accompany the protocols.
e. IRB-approved Informed Consent Forms.
f. HIPAA Authorization ,VA Form 10-0493 (or documentation of waiver of HIPAA authorization).
g. Any proposed amendments and the IRB action on each amendment.
h. Progress reports submitted by Investigators for Continuing Review.
i. Reports of internal or local SAEs and unanticipated problems involving risks to subjects or others.
j. Documentation of protocol deviations.
k. Documentation of noncompliance with applicable requirements.
l. Audit results and documentation of compliance with remediation requirements.
m. Significant new findings: Statements of significant new findings provided to subjects as required in 16.116(b)(5) (38 CFR 16.115(a)(7)).
n. Subject complaints.
o. Summaries of data and safety monitoring findings.
p. All communications with the Investigator, including, but not limited to documentation of all relevant approvals (including continuing review approvals and amendment/modification approvals), documentation of waiver of HIPAA authorization, and documentation of waiver of informed consent or waiver of documentation of informed consent.
q. Data Management and Access Plan (DMAP)

1.3 IRB Administration Documents

The Research Office must maintain and retain all records regarding IRB administrative activities that affect review activities for least five (5) years.

The Research Office must retain all records regarding protocols that are approved and the research initiated for at least five (5) years after completion of the research.

- Rosters of regular and alternate IRB members identified by name, earned degrees, representative capacity, scientific/nonscientific status, affiliation status, and indications of experience sufficient to describe each regular and alternate member's chief anticipated contribution to the IRB's deliberations; and any employment or other relationship between each member and the Durham VAHCS (e.g., full-time employee, part-time employee, WOC, paid or unpaid consultant).
    - Alternate members shall be included on the roster. In addition to the above information, the roster shall indicate the regular member for whom the alternate may substitute.
    - Current and obsolete membership rosters will remain in the Research Office and then archived.
    - The roster of IRB members must be submitted to OHRP by ORO. IRB registrations must be renewed to OHRP and ORO at a minimum every three years. Any changes in Medical Center Director or IRB membership must be reported to OHRP. The responsibility for reporting changes to OHRP usually falls to the Human Research Protection Program Coordinator or the Administrative Officer for Research, respectively.
- Curriculum Vitae or Resume for each voting IRB member. Note: the resume or CV must be updated at the time of appointment or reappointment.
- Maintain current and obsolete copies of the Standard Operating Policies and Procedures.
- Delegation of specific functions, authorities, or responsibilities by the IRB Chairperson must be documented in writing and filed in the Research Office.
- Minutes of IRB, R&D, and SRS Committee meetings.
- Correspondence between the IRB and R&D and SRS Committees.
- Documentation of Human Subjects/Good Clinical Practice and Research Data and Security training requirements.

1.4 Destruction of Copies

All material received by the IRB, which is considered confidential and in excess of the required original documentation and appropriate controlled forms, will be collected at the end of the meeting. Materials will be placed in the secured recycling bins and destroyed according to Medical Center policy.

1.5 Archiving and Destruction

After study closure, all documents and materials germane to IRB determinations will be archived and stored in a secure location. IRB files may be destroyed 6 years after the end of the fiscal year after the research project has been completed or terminated. (Records Schedule: **DAA-0015-2015-0004)**

For research subject to Department of Defense (DoD) regulations, DoD may require submission of records to the Department of Defense for archiving.

Contact the Research Office for guidance and assistance with research record retention.

2. Scope

The policies and procedures apply to all documents used in the submission, initial review, and continuing review of research submitted to the IRB.

3. Responsibility

IRB Program Administrator is responsible for maintaining complete files on all research reviewed by or submitted to the IRB and for all applicable regulatory compliance requirements.

IRB Program Administrator is responsible for overseeing all IRB communications.

IRB Program Specialist is responsible for generating appropriate correspondence in response to IRB meetings and decisions.

IRB Program Support is responsible for distributing IRB correspondence to appropriate parties.

The Medical Center Director is responsible for ensuring meeting space sufficient to provide privacy for conducting IRB meetings, other sensitive duties, and secure storage of records.

RR 401: EXPEDITED REVIEW

1. Policy

An expedited review procedure consists of a review of research involving human subjects by the Chairperson of each IRB or by one or more experienced reviewers designated by the Chairperson from among members of the IRB. An experienced reviewer is an IRB voting member who has completed human subjects protection and Good Clinical Practice training and served as primary reviewer on research protocols for 12 or more IRB meetings, or has completed at least one full term as an R&D member.

1.1 Expedited Review Criteria

The IRB must determine whether or not a study meets expedited review criteria in accordance with the following:

a. An IRB may use the expedited review procedure to review either or both of the following (38 CFR 16.110(b)):

(1) Research in the categories eligible for expedited review <u>and</u> found by the IRB reviewer(s) to involve no more than minimal risk (38 CFR 16.110(b)(1)); or

(2) Minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized (38 CFR 16.110(b)(2)).

Note: Minimal risk is defined as “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” The IRB uses this definition as criteria to determine if risks to subjects are considered minimal. The activities listed should not be deemed to be of minimal risk simply because they are included on the list of eligible research. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

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

c. The IRB must apply the standard requirements for informed consent (or its waiver, alteration, or exception) to all studies that undergo expedited review.

1.2 Expedited Review Eligibility

The IRB may use expedited review procedures to review and approve specific categories of research activities as defined in the Federal Register: Volume 63, Number 216, Pages 60364-60367, November 9, 1998. Studies on marketed drugs that significantly increase the risks or decrease the acceptability of the risks associated with the use of the drugs are not eligible for expedited review. The categories of research activities eligible for expedited review are:

a. **Drugs and Devices (Expedited Review Category 1):** Clinical studies of drugs and medical devices may undergo expedited review only one of the following conditions are met:

(1) The research is on drugs for which an IND application (21 CFR Part 312) is not required.

(2) The research is on medical devices for which an investigational device exemption (IDE) application (21 CFR 812) is not required; or the medical device is cleared or approved for marketing, and the medical device is being used in accordance with its cleared or approved labeling.

b. **Blood Samples (Expedited Review Category 2):** Blood samples are collected by finger stick, heel stick, ear stick, or venipuncture as follows:

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

(2) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kilogram (kg) in an 8-week period, and collection may not occur more frequently than two times per week.

c. **Noninvasive Collection of Biological Specimens (Expedited Review Category 3):** Biological specimens for research purposes are to be collected prospectively by noninvasive means. Examples are as follows:

(1) Hair and nail clippings in a non-disfiguring manner.

(2) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction.

(3) Permanent teeth if routine patient care indicates a need for extraction.

(4) Excreta and external secretions (including sweat).

(5) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue.

(6) Placenta removed at delivery.

(7) Amniotic fluid obtained at the time of rupture of the membrane prior to, or during, labor.

(8) Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.

(9) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.

(10) Sputum collected after saline mist nebulization.

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

(1) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy.

(2) Weighing the subject.

(3) Testing sensory acuity.

(4) Magnetic resonance imaging (MRI).

(5) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography.

(6) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing, where appropriate, given the age, weight, and health of the individual.

e. **Collected Materials (Expedited Review Category 5).** Research involves:

(1) Materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

***NOTE**: Some research in this category may be exempt from the VA regulations for the protection of human subjects (38 CFR 16.101(b)(4)). This listing refers only to research that is not exempt.*

f. **Collection of Data From Voice, Video, or Photographs (Expedited Review Category 6):** See SOP IC 701 for research informed consent requirements for voice, video, and photographic recording.

g. **Group Characteristics, Surveys, Interviews, and Quality Assurance (Expedited Review Category 7).**

Research must be on individual or group characteristics or behavior (including, but not limited to: research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior), or will employ survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. ***NOTE**: Some research in this category may be exempt from the VA regulations for the protection of human subjects (38 CFR 16.101(b)(2) and (b)(3)). This listing refers only to research that is not exempt.*

Note: For research subject to Department of Defense (DoD) regulations, surveys performed on DoD personnel must be submitted, reviewed, and approved by the DoD after the research protocol is approved by the IRB.

1.3 Expedited Review for Continuing Review

The IRB may use expedited review for continuing review under the following circumstances:

a. **Previously-approved Research (Expedited Review Category 8).** Previously-approved Research is research which has previously been approved by the convened IRB where:

(1) No subjects have been enrolled and no additional risks have been identified; or
(2) The research is permanently closed to the enrollment of new subjects; and
  (a) All subjects have completed all research-related interventions; and/or
  (b) The research remains active only for long-term follow-up of subjects; and/or
  (c) The remaining research activities are limited to data analysis.

b. **Minimal-risk Research (Expedited Review Category Number 9).** Minimal-risk research is research not conducted under an IND application or IDE, and where the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk, and no additional risks have been identified.

1.4 Expedited Review Procedures

a. In the expedited review process, the review may be carried out by the IRB Chair or by one or more experienced voting members of the IRB designated by the IRB Chair, in accordance with 38 CFR 16.110(b). If the reviewer feels that there has been a change to the risks or benefits, s/he may refer the study to the full IRB for review.

b. All of the requirements for IRB approval of research apply to expedited reviews.

c. The reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research (38 CFR 16.110(b)). A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in 38 CFR 16.108(b) and 38 CFR 16.110(b) by the convened IRB.

d. The decision and the expedited review eligibility category must be included in the IRB minutes of the next convened IRB meeting and in the letter conveying the IRB's decision to the Investigator.

e. If the expedited review procedure is employed, the date of the continuing review of the research study is based on the date the IRB Chair, or experienced IRB voting member(s) designated by the IRB Chair, gives IRB approval to the research study.

1.5 Notification of the IRB

When the expedited review procedure is used, all regular members are informed of expedited actions taken by the IRB Chairperson or designee by listing the actions on the agenda at the next convened meeting and again in the minutes.

1.6 Documentation

If the study qualifies for expedited review, the IRB Chairperson or designee will document his/her determination of risk and the category and circumstances that justify the use of the expedited procedures.

The minutes will include documentation of the studies that were reviewed via expedited review and any issues resolved relating to questions that IRB members had concerning the research reviewed.

If the IRB Chairperson or designee determines and documents that the patient health record must be flagged in CPRS as participating in research (i.e., a Clinical Warning is required), then the health record must identify the investigator, as well as contact information for a member of the research team that would be available at all times, and contain information on the research study or identify where this information is available.

1.7 Additional Items That May be Reviewed by the Chairperson or Designee

1.7.1 Conditional approval pending minor modifications/revisions

Minor revisions to consent documents and other documentation submitted as a result of full IRB review and as a condition to final approval may be reviewed by the Primary Reviewer(s) or IRB Chairperson. Final approval will be issued providing the revisions, documentation or clarifications do not indicate or result in a change to the specific aims or design of the study or change the risk/benefit ratio.

1.7.2 On-going Continuing review

1.7.2.1 The IRB Chairperson may use the expedited review procedure to review minor changes in previously approved research during the period for which approval is authorized. Any protocol revision that entails more than a minimal risk to the subjects must be reviewed by the full IRB at a convened meeting.

1.7.2.2 Revisions to informed consent documents: Minor changes to informed consent documents that do not affect the rights and welfare of study subjects, or do not involve increased risk or significant changes in study procedures may be reviewed and approved by the Chairperson/designee.

1.7.2.3 Adverse event and safety reports: The IRB Chairperson or designee will review all adverse event reports. If the Chairperson feels that action is needed to protect the safety of research subjects due to the nature or frequency of reported adverse events, he/she may take such action to the full IRB, which will review the adverse events and study in question to determine action, if any, by the IRB. The IRB Reportable

adverse events are defined as an adverse event that is determined to be serious, unexpected and related or possibly related to the research. The Chairperson or designee will review these within 5 days of IRB receipt to determine and document whether actions are warranted to eliminate immediate hazards to subjects. The convened IRB must review these events within 30 days and determine whether the event was Serious and/or Unanticipated and /or Related to the research or not. They may determine that insufficient information was available to make the determination. They must also determine whether revisions to the protocol of informed consent form are warranted.

1.7.2.4 Advertisements: The IRB Chairperson or his/her designee may approve new or revised recruitment advertisements or scripts.

1.7.3 Audit Reports

Research Compliance Officer (RCO) Audit reports may be reviewed by the IRB Chairperson.

1.7.4 Translations

Translations of consent documents will also be submitted for IRB approval and will be reviewed in an expedited manner. There are two options available to obtain approval of translated consent forms.

Option #1: The IRB-approved consent form is translated by the Sponsor or site and submitted to the IRB. The IRB will have a member or consultant fluent in the language of the consent review the translated document for accuracy. It must match the English version. If the translated version does not match the English version, the translator's comments will be submitted with the documents to the next convened IRB

Option #2: The Investigator (or Sponsor) may submit the IRB-approved version of the consent to an IRB-approved, certified translator.

2. Scope

These policies and procedures apply to all initial review, continuing review research and minor modifications to previously approved research submitted to the IRB(s) that qualifies for expedited review. The Chairperson (or designee) will receive and review all relevant material required to be submitted for review at a convened IRB meeting.

3. Responsibility

IRB Program Administrator (or equivalent) is responsible for identifying submissions that qualify for expedited review.

IRB Program Administrator (or staff) will provide a summary via the minutes of expedited review performed to IRB members at convened meetings.

IRB Chairperson (or designee) is responsible for conducting expedited review.

RR 402: INITIAL REVIEW: CRITERIA FOR IRB APPROVAL

1. Policy

All proposed research involving human subjects must be reviewed and approved by the IRB and the R&D committee prior to initiation. The IRB must review the full proposal, the consent form and all supplemental information such as but not limited to the Investigator's brochure and recruiting information. The IRB must evaluate the risks and benefits to subjects to determine that risks are minimized and whether risks to subjects are reasonable in relation to expected benefits. The IRB is not required to perform a comprehensive scientific review of the study, but is responsible for being sufficiently familiar with the science to perform its review, including a sufficient understanding of the science to carry out its responsibilities including, but not limited to, weighing the potential risks and benefits to the subjects. The IRB determines the continuing review interval based on the level of risk for the study. The IRB will perform substantive review of research in convened meetings; a majority of members must agree that the materials under review contain sufficient information for the protocol to receive approval.

The Durham VAHCS IRB should only approve research that supports VHA's mission to advance the health care of our nation's Veterans. Review criteria are based on the principles of justice, beneficence and autonomy as discussed in the Belmont Report and are specified below. In addition, certain other criteria that are unique to Durham VAHCS's system may apply and must be met as well.

1.1 Minimal Criteria for Approval of Research

In order for a research project to be approved, the IRB must find that:

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

B. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result.

    1. In evaluating risks and benefits, the IRB will consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects

of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(1) The IRB must ensure protocols with treatment or services that constitute "usual care" include a narrative section that clearly differentiates the research interventions from usual care, whether usual care is delivered to only some or to all research subjects.

(2) In addition, the IRB must ensure the informed consent process clearly defines for the subject which potential risks are related to the research (38 CFR 16.116(a)(2) and, therefore, needs to be discussed with the research team, versus those associated solely with usual care provided by the subject's health care provider. The informed consent process is to include language advising subjects to review the risks of the latter with their health care providers.

(3) Should an IRB question a protocol's characterization of "usual care," its associated risks, or the person or entity responsible for specific aspects of "usual care," the IRB is to seek clarification from the Investigator and, if warranted, from qualified experts (38 CFR 16.107(f)). The IRB must document its determination(s) accordingly.

2. If the R&D Committee's review of the proposed research yields a different risk determination than made by the IRB; the R&D Committee will request reconsideration of the risks assessment by the IRB. The proposed research will be placed on the next month's IRB agenda. Also the IRB Program Administrator may note a difference in the risks assessment when constructing the minutes, and place the research proposal on the IRB agenda for the next convened meeting.

C. Selection of subjects is equitable: In making this assessment the IRB should take into account the purposes of the research, inclusion and exclusion criteria, and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, employees, or economically or educationally disadvantaged persons (see SOP SC 501). The IRB will consider or request additional information in their

consideration of the scientific and ethical reasons for the exclusion of classes of persons who might benefit from the research.

The IRB will also take into account whether or not the recruitment of non-Veterans is justified and appropriate (see section 1.2 of this SOP).

Recruitment and Advertisements

All recruitment and advertisement materials will be reviewed and approved by the IRB to ensure that enrollment and recruitment practices are fair and equitable. Postings of all advertisements must be limited to the bulletin boards within the Medical Center. General guidance may be posted within VA indicating that veterans may speak with their health care providers if they wish to participate in research and that information on clinical trials is available at http://clinicaltrials.gov, if applicable.

The IRB will review the information content and mode of communication to determine that the procedures are not coercive. The IRB will review the final copy of printed advertisements to assess the relative size and type used and other visual effects. The IRB will review and approve the script for audio and video advertisements, as well as the final taped version. The IRB approves the materials to ensure advertisements are not coercive or create undue influence to the subject to participate. Advertisements must include the word the “Research” and should be limited to information prospective enrollees need to determine their eligibility and interest.

Advertisements for non-VA Research

Advertisements, flyers, and recruitment documents for non-VA research that supports the VHA’s mission and enhances the quality of health care delivery to Veterans may be posted or distributed on VA property as long as the advertisements, flyers, and/or recruitment documents are reviewed by qualified Research Office personnel and meet criteria below.

The submission must include the advertisement/flyer/recruitment document, a detailed abstract, current approved informed consent form, and documentation of current IRB of record approval. Qualified Research Office personnel will review outside requests for the posting of recruiting documents, flyers, and advertisements to ensure that the research is relevant to Veterans, the mission of VA, and will not impede current VA research activities. Non-VA research advertisements will not be reviewed by the IRB or Research Committee as if they are VA research, however, members of these committees may be asked for input as appropriate. The following clear and legible disclaimer will be included on all non-VA research recruitment materials: This is not VA research, will not be conducted by VA, has not been reviewed by VA’s Institutional Review

Board, and is not endorsed by VA. VA is not responsible for any costs incurred by a Veteran if the Veteran enters the study as a research subject. The announcement is being provided for information only. Once these requirements are met, the non-VA research advertisements/flyers/recruitment documents may be posted and/or used in accordance with local policy.

Payment to Subjects

The IRB will review payment arrangements, method of payment, and proposed method and timing of disbursements to limit the risk of coercion, undue influence, and inequitable selection of subjects. Payment must be made from a VA-approved source for funding research activities.

Payment to research participants in studies is not considered a benefit; rather, it should be considered compensation for time and inconvenience associated with participation in research activities, or a recruitment incentive.

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. The IRB will review payment arrangements to participants. Both the method of payment and proposed method and timing of disbursement will be assessed to limit the risks of coercion, undue influence, or inequitable selection of subjects.

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

- No direct subject benefit. When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice in affiliated non-VA institutions is to pay subjects in this situation;
- Others are being paid. In multi-institutional studies, when human subjects at a collaborating non-VA institution are to be paid for the same participation in the same study at the same rate proposed;
- Comparable situations. In other comparable situations in which, in the opinion of the IRB, payment of subjects is appropriate; and

- Transportation expenses. When transportation expenses are incurred by the subject that would not be incurred in the normal course of receiving treatment.

The IRB will determine that:

- Credit for payment accrues as the study progresses and is not contingent upon the subject completing the entire study; and
- Any 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 otherwise would have withdrawn.

The following payment arrangements will not be allowed:

- The entire payment to be contingent upon completion of the entire study; and
- Compensation for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of a product once it has been approved for marketing.

Investigators who wish to pay subjects must, in their proposal, substantiate the proposed payments are reasonable and commensurate with the expected contributions of the subject. In the consent form the terms of the subject participation agreement and the amount and schedule of payments must be included.

When research involves US military personnel, the following limitations on dual compensation apply:

- Individuals are prohibited from receiving pay or compensation for research during duty hours.
- However, US military personnel may be compensated for research if the subject is involved in the research when not on duty.

D. Informed Consent:

- The IRB will ensure that informed consent is obtained from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by appropriate local, state and federal regulations.
- The IRB will ensure that the informed consent form includes all applicable elements of informed consent.
- The IRB will ensure that the informed consent form includes appropriate blocks for signatures and dates.

- The IRB will ensure that the informed consent form is consistent with the protocol and, when relevant, the HIPAA authorization.
- The IRB must determine that the informed consent is appropriately documented as required by local, state, federal, and VA regulations.

E. Safety Monitoring: Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. The plan may include establishing a Data Safety and Monitoring Board or a Data Monitoring Committee as required by DHHS or FDA policy, and a plan for reporting DSMB or DMC findings to the IRB and the sponsor. The IRB will determine whether the safety monitoring plan makes adequate provisions to ensure the safety of the subjects.

F. Privacy and Confidentiality: Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. The IRB determines this through the evaluation of: (1) the methods used to obtain information about subjects and about individuals who may be recruited to participate in studies: (2) and the use of personally identifiable records, and (3) methods to protect the confidentiality of research data, i.e., who will have access to the data, where will the data be stored, how (what media) will it be transferred (if applicable), how long will it be kept and how will it be destroyed. In some cases the IRB may suggest that a Certificate of Confidentiality be obtained to protect the research data. The Investigator submits adequate information at the time of initial review for the IRB to determine if subjects are adequately protected.

G. Information Security: The IRB must determine that applicable VHA and VA information security policies pertaining to research are implemented and continually monitored to ensure compliance as set form in VA Directive 6500 and its handbooks.

H. Vulnerable Subjects: When some or all of the subjects, such as children, pregnant women, prisoners, mentally disabled persons, or employees, are likely to be vulnerable to coercion or undue influence; additional safeguards have been included in the study and in the IRB review process, to protect the rights and welfare of these subjects (See SOP SC 501).

For research subject to Department of Defense (DoD) regulations, the following protections for military research subjects must be in place to minimize undue influence:

- Officers are not permitted to influence the decision of their subordinates.
- Officers and senior non-commissioned officers may not be present at the time of recruitment.

- Officers and senior non-commissioned officers have a separate opportunity to participate.
- When recruitment involves a percentage of a unit, an independent ombudsman is present.

I. Conflict of Interest: The IRB must ensure that steps to manage, reduce or eliminate potential or real conflicts of interest (financial, role (Investigator/patient relationships), and/or institutional) have been taken.

J. Investigator Qualifications: The IRB must determine that the PI and all other Investigators of the proposed research activity have met all current educational requirements for the protection of human research subjects as mandated by the facility's Assurance, VA ORD, funding institutions, and applicable OHRP requirements. The IRB must determine that the Investigator is qualified through education, training, and experience to conduct the research.

K. Time of Review: Studies are reviewed at periods appropriate to the degree of risk research subjects are exposed to due to their participation in the study, but at least annually. To determine which protocols require approval more often than annual, the IRB will use criteria such as:

- the probability and magnitude of anticipated risks to subjects;
- prior experience with the principal Investigator including occurrence of unanticipated problems, noncompliance, complaints from participants and others; involvement of vulnerable populations;
- Involvement of recombinant DNA (including gene transfer); and other protocol specific factors the IRB deems relevant.

L. The IRB must determine if the medical record must be flagged (i.e., whether a Clinical Warning is required) (see SOP RI 803).

1.2 Participation of Non-Veterans in Research

VA research needs to be relevant to Veterans or active duty military personnel. The Investigator must justify including non-Veterans in a VA research protocol, and the IRB must review the justification for inclusion of non-Veterans and specifically approve entering non-Veterans into the study before any non-Veterans can be recruited. The IRB must appropriately document in the IRB minutes or IRB protocol file its' determinations regarding participation of non-Veterans in the study.

a. Outpatient Care for Research Purposes. Any person who is a bona fide volunteer may be furnished outpatient treatment when the treatment to be rendered is part of an approved VA research study and there are insufficient Veteran patients suitable for the study (38 CFR 17.92).

b. Hospital Care for Research Purposes. Any person who is a bona fide volunteer may be admitted to a VA hospital when the treatment to be rendered is part of an approved VA research study and there are insufficient Veteran patients suitable for the study (38 CFR 17.45).

c. Other Research. Non-Veterans may be recruited for studies that will generally benefit Veterans and their well-being but would not include Veterans as subjects. Examples include surveys of VA providers, studies involving Veterans' family members, or studies including active duty military personnel. Although active duty military personnel are not considered Veterans, they should be included in VA studies whenever appropriate.

Active duty military personnel may be entered into VA research conducted jointly by VA and DoD or within DoD facilities. All VA regulations and policies related to Veterans as research subjects apply to non-Veterans entered into VA research. Non-Veterans may not be entered into VA studies simply because a non-Veteran population is easily accessible to the Investigator. Investigators must provide notice of privacy practices and acknowledgement for any non-Veteran enrolled in the approved protocol.

Any greater than minimal risk study that targets non-Veterans for enrollment will be forwarded to the R&DC for review once the IRB has granted the study full approval. Minimal risk studies that target non-Veterans for enrollment may also be forwarded to the R&DC on a case-by-case basis.

1.3 Other Criteria

To ensure the safety of personnel involved in research all research involving biological, chemical, physical, and radiation hazards must be approved by the Research Safety Subcommittee and then receive written approval by the R&D Committee prior to initiation.

The IRB's initial review approval notification must be signed by the Chairperson or the voting member of the IRB who reviewed the research. However, the research must not be initiated until the Investigator has been notified in writing by the ACOS for R&D that all applicable approvals have been obtained and the study may be initiated.

2. Scope

These policies and procedures apply to all IRB staff and members and to research submitted to the IRB.

3. Responsibility

IRB Program Administrator (or equivalent) is responsible for ensuring that IRB reviewers have all the tools and resources they need to complete their research reviews.

IRB Chairperson in conjunction with the IRB Program Administrator is responsible for providing IRB members adequate submission review training and ongoing guidance, and for selecting primary reviewers with the relevant expertise to perform reviews and make necessary recommendations on approval decisions by the IRB.

IRB Reviewer is responsible for conducting a thorough review and making all appropriate approval recommendations for consideration by the IRB.

The Medical Center Director is responsible for ensuring that a procedure is in place to review and approve recruiting documents, flyers, and advertisements for research that is not VA research prior to being posted or distributed in any form within or on the premises of a VA facility. Posting or distributing may include announcing, distributing, publishing, or advertising the study either electronically, by hard copy, or other means to anyone, including Veterans, clinicians, or other staff.

RR 403: CONTINUING REVIEW: ONGOING

1. Policy

No Investigator has a right to conduct research within this institution. Rather, it is a privilege granted by society as a whole and the Medical Center Director of the Durham VAHCS in particular.

The IRB shall conduct continuing review of each human, non-exempt research protocol. This review shall be a substantive assessment for the protection of human subjects, and must consider risk, potential benefits, consent and safeguards. IRB approval may be withdrawn at any time if warranted by the conduct of the research. The regulations authorize the IRB to establish procedures for the concurrent monitoring of research activities involving human subjects. Periodic review of research activities is necessary to determine whether approval should be continued or withdrawn. All research involving human subjects must be reviewed no less than once per year.

IRB approval for the conduct of a study may be withdrawn if the risks to the subjects are determined to be unreasonably high, for example, more than an expected number of adverse events, unexpected serious adverse events, or evidence that the Investigator is not conducting the investigation in compliance with IRB or Institutional guidelines. Such findings may result in more frequent review of the study to determine if approval should be withdrawn or enrollment stopped until corrective measures can be taken or the study terminated. Continuing review includes, but may not be limited to the following activities:

- Investigator audits and third party verification
- Review of all adverse events
- Review of unanticipated problems and protocol deviations
- DSMB or other safety reports
- Amendments
- Review of significant new findings (since last continuing review)
- Reports from employees, staff and faculty
- Noncompliance and complaints

1.1 Investigator Compliance Reviews

The IRB has the authority to observe, or have a third party observe, the informed consent process of research it has approved, and to verify that the study is being conducted as required by the IRB and within the Institutional policies and procedures and site-specific procedures, as appropriate.

The IRB will consider seeking the assistance of an individual to act as a liaison between the Investigator and research subject, or subject's legally authorized representative in

situations where the IRB has determined additional protections are necessary in a vulnerable population. The person's role is to oversee the research consent process in situations where the subject may be vulnerable during the course of the research to ensure the risk of coercion and undue influence is minimized. The IRB may request the individual to observe the informed consent process for the research protocol. The individual must be an impartial third party, unbiased regarding the research and must not be member of the Investigator's research team. The individual may be selected from the hospital's Ethics Committee, research compliance, or a research team member with experience in the consent process but not connected with the proposed research.

IRB staff or members may perform Investigator compliance reviews or use another party to verify information in the study application, or in any interim or continuing review submissions.

The criteria for selecting Investigators to be visited may include:

- Investigators who conduct studies that involve a potential high risk to subjects,
- Studies that involve vulnerable populations,
- Investigators who conduct studies that involve large numbers of subjects,
- Investigators with multiple protocols, and
- Investigators selected at the discretion of the IRB, or
- Investigators randomly selected by the RCO.

Other means of verification include the submission of copies of monitoring reports from Sponsors to the IRB at continuing review.

Investigators may be asked to submit copies of signed informed consent forms, list of enrolled subjects or other documents to ensure their compliance with IRB requirements. The IRB may survey or conduct interviews with screened and/or enrolled subjects as deemed necessary. Investigators are required to submit reports from external audit visits (e.g., Cooperative Studies Program {CSP} studies) to the IRB for review.

1.2 Third Party Verification

The IRB, in protecting the rights and welfare of subjects, may require third party verification of the fact that no change in the research has occurred since the last IRB review. This may be necessary particularly in cooperative studies or other multi-center research. The IRB will consider the following factors in determining when a study requires such verification:

- Probability and magnitude of anticipated risks to subjects;
- Likely medical condition of the proposed subjects;
- Probable nature and frequency of changes that may ordinarily be expected in the type of research proposed;
- Prior experience with the principal Investigator and research team;

- Other factors that the IRB deems relevant.

In making a determination about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period or may retrospectively require such verification at the time of continuing review.

1.3 Reportable Events to the IRB

Unless otherwise specified, events must be reported to the IRB in the annual continuing review submission.

1.3.1 Definitions

1.3.1.1 Adverse Event: an undesirable and unintended, although not necessarily unexpected, result arising during the course of a research protocol (*e.g.*, abnormal physical exam or laboratory finding, headache following spinal tap or intestinal bleeding associated with aspirin therapy). VA's definition: An AE is any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event, including abnormal laboratory finding, symptom, or disease associated with the research or the use of a medical investigation test article. An AE does not necessarily have to have a causal relationship with the research, or any risk associated with the research or the research intervention, or the assessment.

1.3.1.2 Serious Adverse Event: any adverse event that results in any of the following outcomes: (1) Death, (2) a life-threatening event (that places the subject at immediate risk of death from the event as it occurred), (3) inpatient hospitalization or prolongation of existing hospitalization, (4) a persistent or significant disability/incapacity, or (5) a congenital anomaly/birth defect or that requires medical, surgical, behavioral, social or other intervention to prevent such an outcome.

1.3.1.3 Unanticipated (Unexpected): the terms "unanticipated" and "unexpected" refer to an event or problem in VA research that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population.

1.3.1.4 Unanticipated Adverse Device Effect: any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subjects (21 CFR 812.150(a).

1.3.1.5 Protocol Deviation: any departure, alteration, or procedural error in the IRB approved protocol and/or study procedures that occur without prior IRB notification and approval. The cause of the deviation may be within the Investigator's control (e.g., change a protocol procedure or medication), or a deviation may not be in the control of the Investigator (e.g., a subject fails to show-up for a procedure defined in the protocol).

1.3.1.6 Noncompliance: failure to adhere to the local or federal laws, regulations, or policies governing human research.

1.3.1.7 Serious Noncompliance: failure to adhere to the laws, regulations, or policies governing human research that might reasonably be regarded as presenting a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research personnel, or others including their right to privacy and confidentiality of identifiable private information or substantively compromising a facility's HRPP. See examples at *http://www.va.gov/oro/*.

1.3.1.8 Continuing Noncompliance: persistent failure to adhere to the legal and policy requirements, governing human research.

1.3.1.9 Serious Problem. A serious problem is a problem in human research or research information security that may reasonably be regarded as:
(1) Presenting a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research personnel, or others, including their rights to privacy and confidentiality of identifiable private information; or

(2) Substantively compromising a facility's HRPP or research information security program. See examples at *http://www.va.gov/oro/*.

1.3.2 List or summary of events and/or problems that require reporting at Continuing Review

- A summary of all adverse events; protocol deviations (with remediation plans to prevent reoccurrence, if applicable), and unanticipated problems not meeting the definition of immediately reportable. Adverse events that must be reported include any harm experienced by a participant regardless of whether the event was internal (on-site) or external (off-site) and regardless of whether the event meets the FDA definition of 'serious adverse event.'
- A list of all Serious Adverse Events (SAEs) occurring during the review period, including SAEs already reported to IRB. The SAE(s) must include the PI's determination on whether the SAE was unanticipated and/or related to the research.

- Information that indicates a change to the risks or potential benefits of the research. For example:
    1) An interim analysis or safety monitoring report that indicates the frequency or magnitude of harms or benefits may be different than initially presented to the IRB.
    2) Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research.
- A breach of a subject's confidentiality or privacy that involves potential risks to that participant or others.

1.4. Rapidly Reportable Events

1.4.1 Local Research Deaths

VA personnel, including WOC and IPA appointees, must ensure verbal notification of the Institutional Review Board (IRB) immediately upon becoming aware of any local research death that is both unanticipated and related to the research.

(1) The IRB must alert ORO by e-mail or telephone within 2 business days after receiving such notification and provide relevant information as requested. The VA facility Director and the ACOS/R&D must receive concurrent notification.
(2) VA personnel, including WOC and IPA appointees, must ensure written notification of the IRB within 5 business days of becoming aware of the death.
(3) Within 5 business days after receiving written notification of the death, the IRB Chair or a qualified IRB member-reviewer must determine and document whether any actions are warranted to eliminate apparent immediate hazards to subjects.
(4) The IRB must review the death and the determination of the IRB Chair or qualified IRB member-reviewer at its next convened meeting and must determine and document that:

(a) The death was both unanticipated and related to the research; or

(b) There is insufficient information to determine whether the death was both unanticipated and related to the research; or

(c) The death was not unanticipated and/or the death was not related to the research.

(5) Regardless of the determinations the convened IRB must also determine and document whether any protocol or informed consent modifications are warranted. If modifications are warranted, the convened IRB must determine and document whether or not investigators must notify or solicit renewed/revised consent from previously enrolled subjects; and if so, when such notification or consent must take place and how it must be documented. (6) The IRB must notify the VA facility Director and the ACOS/R&D of its determinations within 5 business days of the determinations.

(7) The VA facility Director must report the determinations to ORO within 5 business days after receiving the IRB's notification.

1.4.2 Reporting Local Unanticipated and Related SAEs and Problems

VA personnel, including WOC and IPA appointees, must ensure written notification of the IRB within 5 business days after becoming aware of any local SAE or serious problem that is both unanticipated and related to the research. ***NOTE:*** *For examples, see the ORO Web site* at *http://www.va.gov/oro/.*

These events must be reported to the IRB using the Serious Problem/Adverse Event Related to Research Report Form within 5 business days.

IRB Review of unanticipated SAEs and Serious Problems related to research.
Within 5 business days after receiving written notification of an SAE or serious problem submitted as unanticipated and research related, the IRB Chair or a qualified IRB member-reviewer must determine and document whether any actions are warranted to eliminate apparent immediate hazards to subjects.

The IRB must review the incident and the determination of the IRB Chair or qualified IRB member-reviewer at its **next convened** meeting and must determine and document that:

(a) The incident was serious and unanticipated and related to the research; or

(b) There is insufficient information to determine whether the incident was serious and unanticipated and related to the research; or

(c) The incident was not serious, and/or the incident was not unanticipated, and/or the incident was not related to the research.

Regardless of the determination by the IRB Chair or designated reviewer, the convened IRB must also determine and document whether any protocol or informed consent modifications are warranted. If modifications are warranted, the convened IRB must determine and document whether or not investigators must notify or solicit renewed/revised consent from previously enrolled subjects; and if so, when such notification or consent must take place and how it must be documented.

The IRB must notify the VA facility Director and the ACOS/R&D in writing within 5 business days after its convened meeting if:

(a) Actions were taken to eliminate apparent immediate hazards to subjects; or
(b) The IRB determined that the incident was serious and unanticipated and related to the research, or there was insufficient information to make the determination; or
(c) Protocol or informed consent modifications were warranted.

The VA facility Director must report the situation to ORO within 5 business days after receiving the IRB's notification.

Note: These requirements are in addition to other applicable reporting requirements (e.g., reporting to the sponsor under FDA requirements).

1.4.3 Apparent Serious or Continuing Noncompliance

VA personnel, including WOC and IPA appointees, must ensure that the IRB is notified, in writing, within 5 business days after becoming aware of any apparent serious or continuing noncompliance with IRB or other human research protection requirements. ***NOTE:*** *For examples of apparent serious noncompliance, see the ORO Web site at http://www.va.gov/oro/.*

(1) The convened IRB must review any such notifications at the earliest practicable opportunity, not to exceed 30 business days after the notification. The IRB Chair may take interim action as needed to eliminate apparent immediate hazards to subjects.

(2) The convened IRB must determine and document whether or not serious or continuing noncompliance actually occurred.

(3) If the IRB determines that serious or continuing noncompliance occurred:

(a) A documented IRB determination is also required as to whether remedial actions are needed to ensure present and/or future compliance.

(b) IRB must notify the VA facility Director and the ACOS/R&D within 5 business days after making its determinations.

(c) The VA facility Director must report the determination to ORO within 5 business days after receiving the IRB's notifications.

(d) If the apparent serious or continuing noncompliance was identified by an RCO audit, the IRB must notify the RCO within 5 business days after its determinations, regardless of outcome.

(e) The IRB must track the determinations required under for use in the VA facility Director Certification.

For Department of Defense (DoD) funded studies, issues related to noncompliance by any DoD Component, subordinate, or supported activity shall be referred initially to the next higher management echelon to take deliberate action to resolve. The Investigator must report all findings of serious non-compliance to the Director, Defense Research and Engineering (see DoD Directive 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research") and a copy of that notification must be provided to the Durham VAHCS IRB.

1.5 Amendments/Modifications

Changes in approved research, during the period for which approval has already been given, may not be initiated without prior IRB review and approval (full or expedited review, as appropriate), except where necessary to eliminate apparent immediate hazards to human subjects. The Investigator is required to notify the IRB promptly of any changes made without IRB approval to eliminate apparent immediate hazards to the subject. The notification will be reported as a Protocol Deviation and the IRB will review the modification at a convened meeting to determine that reported changes were consistent with ensuring the subjects' continued welfare.

The *Amendment/Modification Form* plus a separate cover letter describing and justifying the change(s) and all appropriate documentation must accompany the request to review. Required documentation includes a track-changed version of all amended documents (e.g., the protocol, informed consent form, HIPAA authorization/waiver of authorization, phone script, advertisement, survey, or any other item as applicable),and a clean version of all amended documents. The review by the IRB must meet the criteria for IRB approval found at SOP RR 402.

Investigators or Sponsors must submit requests for proposed changes in the research to the IRB in writing. Upon receipt of the proposed protocol change, the Chairperson (or designee), with assistance of the IRB Program Administrator, will determine if the revision is a minor modification. For greater than minimal risk studies, if the change is substantive; i.e., the change represents more than a minimal risk to subjects or major changes to study procedures or data analysis, it must be reviewed and approved by the IRB at a convened meeting in which a Primary Reviewer will be assigned. All members receive all documents submitted in request for a modification. Minor changes to previously approved research, involving no more than minimal risk to the subject, will be reviewed by the expedited review procedure (SOP RR 401-Expedited Review).

A minor modification (based on the judgment of the IRB Chair or designee) is a proposed change in the research related activities that does not alter the risks and benefits of the study and does not change the specific aims or design of the study. Examples include (not limited to):

- The addition of research activities that would be considered exempt or expedited if considered independent from the main research protocol;
- A decrease in the human research subjects' enrollment;
- Narrowing the range of the inclusion criteria;
- Broadening the range of the exclusion criteria;
- Alterations in the dosage of an administered drug, provided the dose and route of administration remain constant (e.g., tablet to capsule or oral liquid);

- Decreasing the number or volume of the biological samples collected, provided that such a change does not affect the collect of information related to safety evaluations;
- Changes to improve the clarity of statements or to correct typographical errors, provided that such changes do not alter the content or intent of the statement;
- Any procedure that is minimal risk and fits the criteria for expedited review categories as outlined in SOP RR 401- Expedited Review.

All proposed protocol modifications/amendments, changes to consent forms (including proposed plans to re-consent), advertisements, recruitment material, questionnaires, Investigator Brochure or package insert changes in study personnel, protocol deviations, and change in study status (e.g., premature completion of the study) must be reported to the IRB. The IRB will determine whether changes to the research activities require a change to the informed consent document and therefore warrant consideration for re-consenting of currently enrolled participants; or whether participants should be notified of significant new information that might affect their willingness to continue participation; or whether notification of participants who have completed interventions is warranted.

The IRB will notify the Investigator of the IRB's decision to approve, disapprove, or require changes to approve the amendments or modifications in writing. The notification by the IRB must be signed by the Chair, a voting member of the IRB, or a member of the IRB staff, before the Investigator may initiate any changes or modifications to the protocol or informed consent form, except when necessary to eliminate immediate hazard(s) to the subject(s).

The date of continuing review is not changed based on the approval date of the amendment unless the IRB specifies that the date of continuing review is changed.

Changes in the PI, LSI, Co-PI, Co-LSI, or investigator of an IRB-approved protocol will be reviewed and approved by the IRB to ensure that the new individual meets criteria described in 38 CFR 16.111.

A greater than minimal risk study amendment that targets non-Veterans for enrollment will be forwarded to the R&DC for review once the IRB has granted the amendment full approval. Amended minimal risk studies that target non-Veterans for enrollment may also be forwarded to the R&DC on a case-by-case basis.

1.6 Significant New Findings

During the course of a study, the IRB may review reports generated from a Data and Safety Monitoring Board (DSMB), adverse event reports, current literature, and other

sources to ascertain the status of the study and assess whether or not the risk/benefit balance is still acceptable. The IRB will determine whether or not new information needs to be conveyed to subjects, or if a segment of the population may be bearing an undue burden of research risk or being denied access to promising therapy.

1.7 Reports from Employees, Staff and Faculty

It is the responsibility of the ACOS/R&D, AO/R&D, RCO, IRB staff and members to act on information, reports, or complaints received from any source that indicate a study being conducted under the jurisdiction of the IRB could adversely affect the rights and welfare of research subjects.

1.7.1 Allegation of Noncompliance

Allegation of noncompliance is defined as an unproven accusation of noncompliance. The Durham VAHCS takes the protection of human subjects very seriously. Failure to comply with the requirements of human subjects' regulations could have very serious consequences resulting in the loss of the Assurance with the Department of Health and Human Services and the ability to conduct research. Durham VAHCS policy requires that noncompliance with federal and/or VA regulations, and local policy affecting human subjects research be promptly (5 working days) reported to the IRB.

The IRB is responsible for determining if serious or continuing noncompliance has occurred. Reports of alleged noncompliance may be received from anyone within or outside the Durham VAHCS but will be sent to the RCO for initial investigation. All reports of inappropriate involvement of human subjects in research will be investigated initially by the RCO to decide whether the allegation requires further action. The allegation will either be designated as not requiring further action, or will be escalated for review by the IRB Chair and convened IRB. A report requires no further action if the reported allegation is not based on facts, is an administrative problem not involving the safety or welfare of human subjects, or is neither serious or continuing noncompliance, nor an unanticipated problem involving risks to subjects or others. The RCO will document whether further action is needed in the applicable protocol file or general IRB file and inform the IRB Chair (or designee).

The RCO will obtain additional relevant information applicable to the allegation (if needed) and review materials central to the allegation after informing the IRB Chair (or designee) for review by the IRB Chair. This information will be initially presented to the IRB Chair (or designee) for review and placed on the IRB agenda for review by the convened IRB at the next scheduled meeting. The IRB Chair (or designee) will also inform the Investigator (if applicable) of the allegation and/or complaint to be reviewed by the convened IRB and obtain additional information as needed. If the allegation and/or complaint require immediate action to be taken as necessary to prevent

unacceptable risk to research subjects, the IRB Chair (or designee) can suspend the study pending review of the incident by the convened IRB.

1.7.2 Research Misconduct

The IRB's responsibility is to protect the rights and welfare of research subjects, which could be placed at risk if there is misconduct on the part of an Investigator or any member of the investigative team. It is, therefore, the duty of the IRB to be receptive to and act on good faith allegations of misconduct.

Allegations of misconduct in science should be referred to the Associate Chief of Staff/Research for handling in accordance with VHA Handbook 1058.2 Research Misconduct and Durham VAHCS policies.

ORO must be notified within one business day (preferably by telephone or email) of any allegation of research misconduct. Subsequent written notification must be provided as specified by ORO Central Office.

1.8 Complaints and Inquiries of the HRPP

As part of its mission to protect the rights, safety, and welfare of human research subjects the Durham VAHCS encourages open communications with research Investigators, research staff, research participants, and the members of the institution to voice complaints, allegations of noncompliance based in fact, and concerns regarding research or the HRPP in general.

The Durham VAHCS encourages reports of possible noncompliance; possible serious problems; making general comments and suggestions; and expressing concerns about other issues or processes involving the HRPP, including the IRB review process and operations to (not necessarily in the following order):

- The ACOS/R&D,
- The AO/R&D,
- The Research Compliance Officer,
- The HRPP Coordinator,
- The R&D Committee Chairperson(s),
- The IRB Chairperson(s).

The institution will respond to complaints, and allegations of research noncompliance based in fact with federal, VA, or institutional policies. The process used to employ this process includes:

- Identifying individuals who have responsibility for responding to questions, concerns, or complaints regarding research protocols, research subjects' rights, and the HRPP.
- Evaluating/investigating each complaint or allegation of noncompliance.
- Ensuring a response to each question, concern, or complaint.
- Taking remedial action as appropriate.

The IRB administrative staff will screen all inquiries and in conjunction with the IRB Chair (or designee) and RCO will make a determination of whether a communication alleges unexpected risks or indicates potential non-compliance. Communications determined to allege unexpected risks or allegations of potential noncompliance will be processed to the IRB and reviewed according to this SOP.

All instances of serious problems and noncompliance will be reviewed, evaluated, investigated and tracked through the IRB until resolved. The results of the investigation will be reported to the R&D committees and Medical Center Director through the IRB and followed up with the complainant. Regulatory authorities or Sponsors may also be notified. Such reports of noncompliance or complaints may come from any source including IRB members, Investigators, research staff, subjects, institutional personnel, the media, anonymous sources or the public.

The IRB has the authority to convene a separate committee to investigate the report of noncompliance. The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB policies, is not in compliance with federal regulations, or has been associated with unexpected serious harm to subjects. All such suspension and or terminations will be reported according SOP CO 601.

1.9 Suspensions and Terminations of IRB Approval

Note that a lapse/expiration of approval is not synonymous to suspension or termination. For more information on lapses of study approval, see SOP RR 404.

Suspension: Suspension refers to a temporary interruption in selected research activities (e.g., new enrollments or specific interventions) due to concerns about the safety, rights, or welfare of human subjects, research personnel, or others, regardless of whether the action to suspend was taken by an investigator, facility official, research review committee, or external entity. Suspension does not refer to interruptions for other reasons, including the expiration of project approval periods.

Termination: Termination refers to a permanent halt in all research activities due to concerns about the safety, rights, or welfare of human subjects, research personnel, or others, regardless of whether the action to terminate was taken by an investigator, facility

official, research review committee, or external entity. Termination does not refer to interruptions for other reasons, including the expiration of project approval periods.

The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB policies, is not in compliance with federal regulations, or has been associated with unexpected serious harm to subjects.

Suspensions and Terminations of Research by the VA Facility: VA facility officials and research review committees must notify the VA facility Director, the ACOS/R&D, and the RCO within 5 business days of suspending or terminating any VA human research study. The VA facility Director must report the suspension/termination to ORO within 5 business days after receiving the notification.

External Suspensions/Terminations of Research: VA personnel, including WOC and IPA appointees, must ensure that the IRB is notified, in writing, within 5 business days after becoming aware of any suspension or termination of VA research by, or at the direction of, any entity external to the facility.
The decision may be made for interim analysis; inadequate drug availability; response to a DSMB report/recommendation; or a pre-planned stopping point; or secondary to changes in the potential risk-benefit ratio to the subjects.

The notification will include whether the interruption is for logistical purposes or for potential risk to subjects or others.

(1) The convened IRB must review the suspension/termination at the earliest practicable opportunity, not to exceed 30 business days after notification, to determine whether it:

(a) Resulted from a local adverse event(s), local noncompliance, or other local issue(s); or

(b) Requires local action (in addition to the suspension/termination) to ensure the safety, rights, or welfare of local human research subjects, personnel, or others or the effectiveness of the DVAHCS HRPP

If the IRB determines that local action in (a) or (b) above applies then:

(a) The IRB must notify the VA facility Director and the ACOS/R&D within 5 business days after the determination;

(b) The VA facility Director must report the suspension/termination to ORO within 5 business days after receiving the IRB's notification.

The IRB will consider additional restrictions as appropriate. The Investigator will cease research activity as specified. The Investigator will notify the IRB upon notification from the sponsor of a reinstatement of research activity.

Other entities will be notified as documented in SOP CO 601. The IRB Chairperson is authorized to temporarily halt any IRB approved research activity in whole or part pending additional information or whenever credible evidence justifying such suspension or termination is received.

If the Medical Center Director or someone other than the IRB Chairperson suspends or terminates a study, it must be reported to the IRB and reviewed by the convened IRB.

Following an IRB determination to suspend or terminate IRB approval, the IRB at a convened meeting will review Investigator proposed procedures or make additional recommendations for an orderly cessation of research activities to ensure the safety and welfare of subjects by including some or all of the following additional activities:

- Notifying current subjects in writing of the suspension or termination through IRB approved communication;
- Making arrangements for appropriate medical care during the suspension or termination;
- Notify former subjects in writing when the reason for the suspension or termination may impact their safety or welfare;
- Inform subjects of any required follow-up procedures required by the IRB;
- Report adverse events/unanticipated problems involving risks to subjects or others, suspensions or terminations, to sponsor or FDA if applicable.

The following entities will be also notified concurrently as applicable:

- R&D Committee;
- ORD, if VA-funded;
- Privacy Officer, when reports involve unauthorized use, loss, or disclosure of III patient information;
- Information Security Officer when reports involve violations of information security requirements;
- OHRP when the research is regulated by DHHS;
- FDA when the research is FDA regulated; and
- Other federal agencies who oversee the research.

1.10 Administrative Hold

An administrative hold is a voluntary interruption of research enrollments and ongoing research activities by an appropriate facility official, research Investigator, or sponsor (including the VHA ORD when ORD is the sponsor). Administrative hold does <u>not</u> apply to interruptions of VA research related to concerns regarding the safety, rights, or welfare of human research subjects, research Investigators, research staff, or others. Note: an administrative hold must not be used to avoid reporting deficiencies or circumstances that otherwise require reporting by federal agencies.

1.11 Unapproved Research

When unapproved research is discovered, the IRB and the institution will act promptly to halt the research, ensure remedial action regarding any breach of regulatory or institutional human subject protection requirements, and address the question of the Investigator's fitness to conduct any future human subject research. Reporting the finding as serious noncompliance would be required.

1.12 Research Information Protection Incidents

1.12.1 Immediate Reporting

RESEARCH INFORMATION SECURITY**:** VA personnel, including WOC and IPA appointees, should email VHADURResearchEventReport@va.gov (this account includes the ACOS-R&D, ISO, PO, RCO, AO- R&D, MCD, IRB and R&DC Chairs) also notify any relevant investigators immediately (i.e., within one hour) upon becoming aware of any information security incidents related to VA research, including any inappropriate access, loss, or theft of PHI; noncompliant storage, transmission, removal, or destruction of PHI; or theft, loss, or noncompliant destruction of equipment containing PHI.

The ACOS/R&D must immediately notify the records management official if VA records were destroyed.

These events also require a separate written IRB report form entitled Report of Privacy and/or Information Security Incidents in VA Research.

1.12.2 Additional Reporting Requirements:

The VA facility Director must report the following circumstances related to research information security incidents to ORO within 5 business days after taking or becoming aware of such action(s), regardless of any IRB determination.

(1) Provision of an Issue Brief for VA Central Office regarding the incident;

(2) Any notification to individual(s) of an information breach or provision of credit monitoring as required by the Network Security Operations Center (NSOC);

(3) Any breach notification required under the Health Information Technology for Economic and Clinical Health (HITECH) Act;

(4) Any notification to or from the Office of Inspector General (OIG) regarding the incident.

2. Scope

These policies and procedures apply to all research submitted to the IRB.

3. Responsibility

IRB Program Administrator or equivalent is responsible for establishing the processes for conducting ongoing reviews of research.

IRB Chairperson (or designee) is responsible for preliminary assessments of adverse events, significant new findings and the need for third party verification.

Principal Investigators are responsible for ensuring that (1) all human subject research that they conduct as employees or agents of VHA has received initial prospective review and approval by an IRB; (2) continuing review and approval of the research has been accomplished within the time frame stipulated by the IRB; and (3) the research is conducted at all times in compliance with all applicable regulatory requirements and the determinations of the IRB. No changes in approved research may be initiated without prior IRB approval, except where necessary to eliminate apparent immediate hazards to subjects; and no research may be continued beyond the IRB-designated approval period.

RR 404: CONTINUING REVIEW: CRITERIA FOR RENEWAL

1. Policy

The IRB conducts continuing review of research taking place within its jurisdiction at intervals appropriate to the degree of risk, but not less than once per year. There shall be no grace period beyond the approval period granted by the IRB which shall not exceed one year (365 days). Research that continues after the approval period expires is research conducted without IRB approval.

Timely submission of a research protocol for continuing review is the responsibility of the Investigator. If continuing review does not occur within the timeframe set by the IRB, the IRB approval for the research automatically expires. Enrollment for new subjects cannot occur.

The same considerations for IRB review as described in SOP RR 402 apply to continuing review. The IRB uses the primary reviewer process for continuing review not meeting expedited criteria. Prior to the convened meeting, the IRB Chair or designee shall be provided with detailed continuing review materials sufficient to conduct substantive and meaningful reviews.

1.1 Interval for Review for Purposes of Renewal

The IRB must conduct continuing review of protocols for purposes of renewal of the IRB approval period, at intervals appropriate to the degree of risk, which is determined at the initial review, but not less than once per year. “Not less than once per year" means that the research must be reviewed on or before the one-year anniversary of the previous IRB review date, even though the research activity may not have begun until sometime after the IRB granted approval. The expiration date represents the last day that research activity can be conducted.

Investigators are responsible for requesting re-approval in anticipation of the expiration of the approval period. Investigators are required to submit a periodic report prior to the expiration of the study or as specified by the IRB, but at least annually. Investigators will receive a notification from the Research office at 60 and 30 days prior to the expiration of the approved protocol. The report should normally be filed 60 days before the study approval period ends.

1.2 Extensions of Approval Period

There is no grace period extending the conduct of the research beyond the expiration date of IRB approval.

1.3 Criteria for Renewal

Continuing review must be substantive and meaningful. When considering whether or not to renew a study, the IRB revisits the same criteria used to grant initial approval. Therefore, the IRB (or the reviewers for protocols reviewed under an expedited procedure) must evaluate risks and anticipated benefits and determine that:

- The risks to subjects continue to be minimized
- Risks to subjects are reasonable in relation to the anticipated benefits;
- The selection of subjects continues to be reasonable in relation to anticipated benefits;
- Informed consent continues to be appropriately documented;
- Additionally, there are:
    - Provisions for safety monitoring of the data,
    - Protections to ensure the privacy of subjects and confidentiality of data, and
    - Appropriate safeguards for vulnerable populations.

Because it may be only after research has begun that the real risks can be evaluated and the preliminary results used to compute the actual risk/benefit ratio; the IRB can then determine whether or not the study can be renewed at the same risk/benefit ratio, or if new information has changed that determination. The IRB will determine the interval of continuing review based on the evaluation of the risk/benefit ratio.

In order to determine the status of the study, the Investigator must submit to the IRB a protocol summary (this may be in the form of an abstract) and a written status report that includes:

(1) A brief summary of the research methodology;

(2) The number of subjects entered and withdrawn (including the reason for withdrawal) for the review period and since the inception of the research study;

(3) A summary of complaints regarding the research since the last IRB review;

(4) The gender and minority status of those entered into the protocol, when appropriate;

(5) The number of subjects considered to be members of specific vulnerable populations;

(6) A copy of the current informed consent form (or all current informed consent forms if there is more than one) and any new proposed informed consent form along with a description of changes in the new form (i.e., track changes);

(7) A copy of the current HIPAA authorization document;

(8) A list of all amendments to the protocol since the last IRB initial or continuing review and approval;

(9) Information that may impact on the risk benefit ratio, such as SAEs and complaints regarding the research;

(10) Summaries, recommendations, or minutes of the DMC meetings (if applicable) or findings based on information collected by the data and safety monitoring plan submitted in the initial proposal;

(11) An assurance that all identified unanticipated internal or local SAEs, whether related or unrelated to the research, have been reported as required to the IRB of record (see VHA Handbook 1058.01);

(12) A summary of all unanticipated problems involving risks to subjects or others, and all internal or local SAEs;

(13) Research findings to date, if available;

(14) Any relevant multi-center trial reports;

(15) New scientific findings in the literature, or other relevant findings, that may impact on the research; and

(16) A statement signed by the PI certifying that all subjects entered onto the master list of subjects for the study signed an informed consent form prior to undergoing any study interactions or interventions, unless the IRB has granted a waiver of informed consent (38 CFR 16.116(c) and (d)), or a waiver of the signed informed consent form (38 CFR 16.117(c)).

Continuing IRB review is also required as long as individually identifiable follow-up data are collected on subjects enrolled in the protocols at participating sites. The IRB is required to review any multicenter trial reports. This remains the case even after a protocol has been closed at participating sites and protocol-related treatment has been completed for all subjects. These renewal requests may qualify for expedited review.

1.4 IRB Review

All IRB members (both voting and nonvoting, and ex officio) need to, at a minimum, receive, and review a protocol summary and a status report on the progress of the research. At least one voting member of the IRB (i.e., a primary reviewer) also needs to receive a copy of the complete protocol, including any modifications previously approved by the IRB. Furthermore, upon request, any IRB member also needs to have access to the complete IRB protocol file and relevant IRB minutes prior to or during the convened IRB meeting.

(1) The IRB must ensure that all approval criteria are satisfied.

(2) The IRB must ensure that the currently approved or proposed informed consent document remains accurate and complete and contains all required elements including appropriate blocks for signatures and dates and, if applicable, that the informed consent form and the HIPAA authorization are consistent with each other and with the protocol.

(3) The IRB must ensure that any significant new findings that may affect the subject's willingness to continue participation are provided to the subjects.

(4) When reviewing continuing research under an expedited review procedure, the IRB Chair or designated voting IRB member(s) should receive and review all the above referenced documentation, including the complete protocol.

(5) The IRB must ensure that the master list of subjects entered into the study contains only those subjects who have signed an informed consent form unless the IRB has granted a waiver of informed consent (38 CFR 16.116(c) and (d)), or a waiver of the signed informed consent form (38 CFR.117(c)). The IRB may rely on assurances from the PI and audits conducted by the RCO.

When continuing review occurs annually and the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur.

Any continuing review application of a greater than minimal risk study that targets non-Veterans for enrollment will be forwarded to the R&DC for review once the IRB has granted the study full continuing approval. Minimal risk studies that target non-Veterans for enrollment may also be forwarded to the R&DC for continuing review on a case-by-case basis.

1.5 Possible Outcomes of Continuing Review

As an outcome of continuing review, the IRB may approve the research to continue, require that the research be modified, or halted altogether. The IRB may need to impose special precautions or relax special requirements it had previously imposed on the research protocol.

1.6 Expiration of IRB approval

A lapse in study approval may occur for several reasons: the PI did not submit (or submitted too late) a continuing review application, the PI's response to an IRB contingency was not received and/or approved prior to the study expiration date, or other administrative reasons. In addition to the 60- and 30-day reminders that expiration will soon occur, the Research Office will make a reasonable attempt(s) via letter, phone call, or e-mail to inform the PI that his/her study approval will soon lapse. Should approval lapse, the Research Office will send a letter of notification to the PI.

If the continuing review does not occur within the timeframe set by the IRB, the IRB approval for the research automatically expires. If approval expires, the investigator must:

1) Stop all research activities including, but not limited to, enrollment of new subjects, analyses of individually identifiable data, and research interventions or interactions with currently participant subjects, except where stopping such interventions or interactions could be harmful to those subjects, and
2) Immediately submit to the IRB Chair a list of research subjects who could be harmed by stopping specified study interventions or interactions. The IRB Chair must determine within 2 business days whether or not such interventions or interactions may continue.

If the Investigator is in communication with the IRB, the Continuing Review Report or other report is forthcoming, and in the opinion of the IRB Chair (who may consult with the Chief of Staff), subjects participating in such a study would suffer a hardship if medical care were discontinued, there is an overriding safety concern, or ethical issue present, appropriate medical care or the research intervention may continue beyond the expiration date for a reasonable amount of time (usually 30 days). However, new subjects cannot be enrolled. The IRB will address on a case-by-case basis those rare instances where failure to enroll new subjects would seriously jeopardize the safety or well-being of an individual. Prospective research data cannot be collected, and no procedures that are only being performed for the purposes of the protocol may be performed until a Continuing Review Report or other progress report is reviewed and approved.

In order for the study to regain approval, the PI must submit a memo stating whether or not any study activities occurred during the approval lapse and/or must respond to

outstanding contingencies. Once the Research Office receives required documentation, the study will undergo a review at the next convened meeting. The IRB review and documentation in the minutes will indicate that this is a continuing review to reinstate the study and re-set the annual continuing review date.

The IRB cannot retrospectively grant approval to cover a period of lapsed IRB approval. The IRB will require the Investigator to report the lapse in approval to the sponsor (if applicable) and provide written documentation of such report.

The IRB may review a list of expired studies at convened meetings.

1.7 Expedited Review for Renewal

A protocol that was originally reviewed using the expedited review procedure may receive its continuing review on an expedited basis. Additionally, a protocol reviewed by a convened IRB that had no accrual to date and no additional risks have been identified, or is permanently closed to new subjects AND all subjects have completed research-related interventions AND the study is open only for long term follow-up of subjects, or which remains open only to data analysis or the collection of private identifiable information requires annual review, may be reviewed using an expedited review.

A protocol that was initially reviewed at a convened meeting and determined by the IRB to be no more than minimum risk and meet at least one of the criteria for expedited review may receive continuing review using the expedited review procedure.

When conducting review under an expedited review procedure, the IRB Chairperson or designated IRB member conducts the review on behalf of the full IRB using the same criteria for renewal as stated in section 1.3 of this policy. If the reviewer feels that there has been a change to the risks or benefits, he or she may refer the study to the full IRB for review.

1.8 IRB Documentation of Continuing Review

The IRB will notify the Investigator, the R&D Committee, and the local research office in writing of its determination to approve, disapprove, or require changes to approve the continuing review. The notification by the IRB must be signed by the IRB Chair, another voting member of the IRB, or a member of the IRB staff.

2. Scope

These policies and procedures apply to all research submitted to the IRB.

3. Responsibility

IRB Chairperson or IRB Program Administrator is responsible for establishing and implementing processes for making research renewal decisions.

The Investigator is responsible for timely and complete continuing review submissions.

RR 405: STUDY COMPLETION

1. Policy

The completion or termination of the study is a change in activity and must be reported to the IRB. Investigators must submit a notice of study termination in the form of a memorandum along with a progress report and information of subject experiences to the Research office. Although subjects will no longer be "at risk" under the study, a final report/notice to the IRB allows it to close its files as well as providing information that may be used by the IRB in the evaluation and approval of related studies.

1.1 Determining When a Project Can be Closed

When individually identifiable follow-up data are no longer being collected on subjects enrolled in a protocol and analysis that could indicate new information is complete, the study may be closed.

Multi-site industry sponsored studies may be closed when the Investigator submits his or her final report to the sponsor.

Multi-site non-industry sponsored studies may be closed when the participating Investigator is no longer collecting individually identifiable follow-up data on subjects enrolled. If the Investigator anticipates that the site initiating the study will need additional follow-up data, the study should remain open. If a participating site needs follow-up data from a site with a closed study, the Investigator must submit a new submission to the IRB for approval to open the closed study.

1.2 Completion Reports

Investigators are responsible for submitting termination reports once the study is completed or terminated. Investigators must submit a progress report to date, and information regarding subject experiences (number enrolled, problems, adverse events) since last IRB review. The notification will be placed on the agenda of the next convened meeting. However, if at the time of the Continuing Review the continuation report paperwork identifies that the study is complete, it will be reviewed as continuing review that is terminated. Study closures for which no enrollment occurred, and only subject follow-up or data analysis was being conducted since last continuation review may receive expedited review.

2. Scope

These policies and procedures apply to all research submitted to the IRB.

3. Responsibility

The Program Administrator (or equivalent) is responsible for ensuring all study completion documentation is received, reviewed, presented to the IRB, and filed appropriately.

The Investigator is responsible for closing studies when appropriate.

RR 406: CATEGORIES OF ACTION

1. Policy

The IRB, at a convened meeting of a quorum, must review all protocols that involve more than minimal risk to human subjects. As a result of its review, the IRB may decide to approve or disapprove the proposed research activity, or to specify modifications required to secure IRB approval of the research activity. Except when the expedited review procedure is used, these actions will be taken by a vote of a majority of the regular and alternate members present, except for those members present but unable to vote in accordance with the IRB's conflict of interest policies. When reviewed via expedited review, the Chairperson or designee can take any of the following actions except to disapprove a study.

In instances where the IRB is being informed of an item or event, the IRB may acknowledge the item or event without taking a vote. Such instances include, but are not limited to: old business items, new business items, notifications, RCO audit reports, etc.

1.1 Determinations

The IRB may make one of the following determinations as a result of its review of research submitted for initial review or for continuing review:

A. Approved (with no changes): The protocol and accompanying documents are approved as submitted. Final approval will commence on the day the study is approved by an action of the convened IRB or Chairperson or designee (for expedited reviews) and will expire within one (1) year of the meeting date, but not later than the day preceding the date of review unless otherwise specified by the IRB. Research may not begin until the approval has been granted by the R&D Committee.

   Approvals are always considered conditional. The conditions for continued approval, and the time frame (if any) within which they must be met will be clearly stated in the approval letter. If the conditions of the approval are not met, approval may be withdrawn.

B. Contingent Approval (minor changes): Minor modification of, or addition to, a protocol or accompanying document(s) is required. Changes will be voted upon during the IRB's meeting, as well as the terms of approval. The Investigator will be informed in writing of the recommended changes and requested information and must provide the IRB with the changes or information. The study cannot proceed until subsequent review and approval of the material submitted in the investigator's response to the minor conditions specified by the convened IRB.

The IRB Chairperson or designee, the primary reviewer or another person delegated by the IRB has the authority to review the information submitted by the Investigator in response. Upon satisfactory review, approval will be issued as of the date the protocol was initially reviewed at the convened meeting. The expiration date of IRB approval will be based on the anniversary date of the initial IRB review. Subjects must not be recruited into the study until the R&D Committee has issued final approval.

The approval of minor modifications by the Chair or designated IRB voting member must be documented in the minutes of the first IRB meeting that takes place after the date of the approval of the minor modifications.

C. Deferred (Deferred pending receipt of additional information): Significant questions are raised by the proposal because the IRB determines that it lacks sufficient information to reach a decision, requiring its reconsideration after additional information is received from the Sponsor and/or Investigator. The resubmission must be reviewed by a convened IRB. (Deferred is used for this category at the Durham VAHCS because the IRB database in use (MIRB) does not allow for a vote count for Deferred).

D. Tabled (Requires substantive changes also referred to as Contingent Approval requiring substantive changes): Substantial modification of, or addition to, a protocol or accompanying document(s) is required. Changes will be voted upon during the IRB's meeting, as well as the terms of approval. The Investigator will be informed in writing of the recommended changes and requested information and must provide the IRB with the changes or information.

Material or information must be reviewed by the IRB at a convened meeting. Approval will be issued as the date of the convened IRB meeting in which satisfactory submission of IRB recommendations was received. The expiration date of the IRB approval will be based on the anniversary date of the convened meeting in which satisfactory submission of IRB recommendations was received. Subjects must not be recruited into the study until the R&D Committee has issued final approval.

E. Disapproval: The proposal fails to meet one or more criteria used by the IRB for approval of research and the IRB has determined that the research, as presented, cannot be conducted at the facility. Disapproval cannot be given through the expedited review mechanism and may only be given by majority vote at a convened meeting of the IRB. The Investigator will be notified in writing of the IRB's decision to disapprove the research as presented. The notification will be signed by the IRB Chairperson of another voting member of the IRB. The reason(s) for the IRB's disapproval will be provided and the Investigator will be given the opportunity to respond in person, or in writing, and/or to rewrite the proposal (if applicable).

Note: An IRB-approved research activity may be disapproved by the R&D Committee, the Medical Center Director, or the ORD. If a research activity is disapproved by the IRB, the R&D Committee, or any higher authority, the Investigator's institution cannot overrule the decision. The R&D Committee and higher authority may strengthen requirements and/or conditions, or add other modifications to secure R&D approval or approval by a higher authority. Previously approved research proposals and/or consent forms must be re-approved by the IRB before initiating the changes or modifications.

1.2 Investigator Appeal of IRB Action

An Investigator may appeal the revisions required by the IRB in the protocol and/or informed consent form. This appeal must be in writing and submitted to the IRB Program Administrator. Investigators may also appeal an IRB decision to disapprove a study. Any such appeal may be in writing or in person and must be reviewed by the full IRB at a convened meeting. If the appeal is denied and the study disapproved, the Investigator's institution cannot override the IRB's decision.

An Investigator may re-submit protocols disapproved by the IRB as an initial review. All IRB concerns and reasons for disapproval must be addressed in the re-submission.

2. Scope

These policies and procedures apply to all research submitted to the IRB.

3. Responsibility

Program Administrator, RCO, ACOS/R&D (or equivalent), is responsible for ensuring that all IRB decisions and actions are based on institutional and regulatory requirements.

IRB Chairperson (or designee) is responsible for ensuring the appropriateness of all IRB decisions and actions.

RR 407: PRIVACY OFFICER & INFORMATION SECURITY OFFICER REVIEWS

1. Policy

The Privacy Officer (PO) and the Information Security Officer (ISO) are responsible for the reviewing all research protocols at the Durham VAHCS.

A VA facility Privacy Officer and a VA facility Information Security Officer must serve in an advisory capacity to the IRB as either non-voting members or as consultants. ***NOTE**: The facility PO and ISO must be involved in the review of human subjects research to address and mitigate potential concerns regarding privacy and confidentiality, and information security, respectively.*

1.1 Responsibilities

A. Ensuring the proposed research complies with all applicable local, VA and other Federal requirements for privacy and confidentiality, and for information security, respectively, by identifying, addressing, and mitigating potential concerns about proposed research studies.

B. Reviewing the proposed study protocol and any other relevant materials submitted with the IRB application.

C. Identifying deficiencies in the provisions for privacy and confidentiality or information security, respectively, of the proposed research, and making recommendations to the investigator and/or the IRB of options available to correct the deficiencies.

D. Following up with the Investigator, in a timely manner, to ensure the proposed research is in compliance with relevant privacy and confidentiality, and information security requirements, respectively, <u>before</u> the Investigator initiates the study.

E. A final review is required only after the IRB has approved the study to ensure no further changes impact the privacy and security requirements of this study. *NOTE: The ISO and PO final review may occur by virtue of the ISO and PO participation at IRB convened meetings.*

2. Scope

This applies to all research conducted at the Durham VAHCS.

3. Responsibility

ISO and PO must ensure that proposed research complies with all applicable local, VA and other Federal requirements for privacy and confidentiality and for information security.

Investigators are responsible for submitting proposed research and proposed research changes to the ISO and/or PO for review prior to submitting the research to the Research Office for IRB review.

SC 501: VULERNABLE POPULATIONS

1. Policy

Not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Some persons are in need of extensive protection, even to the point of excluding them from activities that may harm them. Other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. Indeed, some types of research may, in and of themselves, create a vulnerable group – that is, the subjects lose their autonomy or are exposed to unknown risks. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

The IRB is required in accordance with 38 CFR 16.111(b), 45 CFR 16.111(b) and 21 CFR 56.111(b) to give special consideration to protecting the rights and welfare, and ensuring additional safeguards are in place when some or all of the subjects are likely to be vulnerable to coercion or undue influence.

Whenever VA has more stringent requirements than DHHS for protection of vulnerable individuals or vulnerable populations as research subjects, all VA requirements must be met.

1.1 Documentation of Vulnerability

Where relevant, the IRB needs to document why it considers an individual or population to be vulnerable, and that adequate safeguards have been included in the study to protect the rights and welfare of subjects who are likely to be vulnerable. Individuals or populations that may be temporarily or permanently vulnerable include, but are not limited to, those who:

(1) Are susceptible to coercion or undue influence (e.g., the homeless, prisoners, students, patients with limited or no treatment options, socially and economically disadvantaged).
(2) Lack comprehension of the research and its potential risks (e.g., educationally disadvantaged, dementia, schizophrenia, depression).
(3) Have increased susceptibility to harm from the procedures of the specific study under review (e.g., individuals who would have to answer study survey questions about their sexual assault).
(4) Are at risk for economic, social, or legal consequences from the study (e.g., individuals who would have to answer study survey questions about their drug use or HIV status).

1.2 Populations Considered to be Categorically Vulnerable

While all protocols need to be assessed for vulnerability of subjects within the context of the specific protocol, the populations named in this subparagraph must always have additional protections. VA considers the following populations to be categorically vulnerable:

(1) Fetuses
(2) Neonates
(3) Pregnant women
(4) Prisoners
(5) Children
(6) Subjects who lack decision-making capacity

1.3 Populations in Which Research is Not Allowed

1.3.1 Fetuses

Research in which the focus is either a fetus, or human fetal tissue, in-utero or ex-utero (or uses human fetal tissue), must not be conducted by VA Investigators while on official duty, or at VA facilities, or at VA approved off-site facilities. Use of stem cells shall be governed by the policy set by NIH for recipients of NIH research funding.

1.3.2 Neonates

VA investigators cannot conduct interventions in research that enroll neonates while on official duty, or at VA facilities, or at VA-approved off-site facilities. Note: Prospective observational and retrospective record review studies that involve neonates or neonatal outcomes are permitted.

1.3.3 In Vitro Fertilization

Research that involves provision of in vitro fertilization services cannot be conducted by VA Investigators while on official duty, or at VA facilities, or at VA-approved off-site facilities. Note: Prospective and retrospective studies that enroll or include pregnant subjects who conceived through in vitro fertilization or other artificial reproductive technologies are permitted.

1.3.4 Prisoners of War

For research subject to Department of Defense (DoD) regulations, research involving prisoners of war is prohibited. Note: The IRB must be aware of the definition of “prisoner of war” for the DoD Component granting the addendum.

1.4 Prisoners

Prisoner is defined as: An individual involuntarily confined in a penal institution, including persons: (1) sentenced under a criminal or civil statue; (2) detained pending

arraignment, trial, or sentencing; and (3) detained in other facilities (*e.g.*, for drug detoxification or treatment of alcoholism) under statutes or commitment procedures providing such alternatives to criminal prosecution or incarceration in a penal institution [45 CFR 46.303(c)].

Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.

Common examples of the application of the regulatory definition of prisoner are as follows:

- Individuals who are detained in a residential facility for court-ordered substance abuse treatment as a form of sentencing or alternative to incarceration are prisoners; however, individuals who are receiving non-residential court-ordered substance abuse treatment and are residing in the community are not prisoners.
- Individuals with psychiatric illnesses who have been committed involuntarily to an institution as an alternative to a criminal prosecution or incarceration are prisoners; however, individuals who have been voluntarily admitted to an institution for treatment of a psychiatric illness, or who have been civilly committed to nonpenal institutions for treatment because their illness makes them a danger to themselves or others, are not prisoners.
- Parolees who are detained in a treatment center as a condition of parole are prisoners; however, persons living in the community and sentenced to community-supervised monitoring, including parolees, are not prisoners.
- Probationers and individuals wearing monitoring devices are generally not considered to be prisoners; however, situations of this kind frequently require an analysis of the particular circumstances of the planned subject population. The Durham VAHCS and/or its Investigators may consult with OHRP when questions arise about research involving these populations.

The Durham VAHCS does not conduct research involving prisoners. Prisoners are considered a vulnerable population because both their incarceration and the constraints imposed on them during their incarceration may render them unable to make a truly informed and voluntary decision regarding whether or not to participate as subjects in research. Therefore research involving prisoners must not be conducted by a VA Investigator while on official duty, at VA facilities, or at VA-approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer (CRADO). If the waiver is granted, the research must be in accordance with applicable Federal regulations pertaining to prisoners as research subjects (see 45 CFR Part 46, Subpart C, Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects).

1.4.1 When Subjects Become Prisoners During a Research Protocol

This policy applies whenever any human subject in a research protocol becomes a prisoner at any time during the protocol, *e.g.,* after the research has commenced. This is necessary because it is unlikely that review of the research and the consent document contemplated the constraints imposed by the possible future incarceration of the subject.

If a subject becomes a prisoner after enrollment in research, the Principal Investigator is responsible for reporting this situation in writing to the IRB immediately (within 10 days of discovery) as an unanticipated problem.

The Investigator must make a determination as to whether or not it is in the best interests of the subject to remain in the study, or if the subject can be safely withdrawn from the study.

If the Investigator determines it is in the best interest of the subject to remain in the study, the subject's continued participation in the study is contingent on the IRB's review and approval of such participation. The IRB approval must comply with 45 CFR 46.301-306.

The IRB can approve the request and require the Investigator to seek approval from the CRADO in accordance with applicable Federal Regulations pertaining to prisoners as research subjects, or determine that this subject must be withdrawn from the research (most likely scenario). If the research involves a treatment unavailable except in the research study, the Investigator will be encourage to locate an approved protocol (with prisoner representative) at another location willing to enroll the subject. ***Note:*** *Subsequent approval of prisoner research by the CRADO will require the Durham VAHCS IRB to become duly constituted with a prisoner representative to review prisoner research and follow Subpart C.*

Additionally, the IRB should confirm that, when appropriate, the informed consent process includes information regarding when subsequent incarceration may result in termination of the subject's participation by the Investigator without regard to the subject's consent.

After IRB and other relevant approvals (e.g., from the penal system) for the incarcerated subject's continued participation in the study have been obtained, a waiver must also be obtained from the CRADO.

If the Investigator becomes aware of an incarceration after the participant has been released from the penal institution, the IRB does not need to comply with 45 CFR 46 Subpart C or obtain a waiver from CRADO. The Investigator will report the incarceration

as a protocol deviation at the next continuing review. Becoming aware of the incarceration after the participant has been released from the penal institution does not require immediate reporting to the IRB (within 10 days of discovery) as an unanticipated problem.

If the Investigator becomes aware of a pending or future incarceration and withdraws the participant prior to entering the penal institution, the Investigator will report this withdrawal at the next continuing review.

1.5 Children

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

1.5.1 Requirements

The VA is authorized to care for Veterans and to conduct research that supports the mission of VHA and that enhances the quality of health care delivered to Veterans. Therefore, research involving children must be reviewed carefully by the IRB for its relevance to VA and must not be greater than minimal risk. The VA medical facility Director must approve participation in the proposed research that includes children. Note: Research involving biological specimens or data obtained from children is considered to be research involving children even if de-identified. If the biological specimens or data were previously collected, they must have been collected under applicable policies and ethical guidelines. If the waiver is granted, the research must be in accordance with applicable Federal regulations pertaining to children as research subjects (see 45 CFR Part 46, Subpart D, Additional Protections for Children Involved as Subjects in Research).

1.5.2 Application

To conduct research involving children, the following information must be submitted to the IRB for each protocol:

(1) A cover letter signed by the Investigator that contains the following information:

(a) Evidence that the facility is able to respond to pediatric emergencies if the study includes an interaction with children at the VA facility.

(b) Any additional safeguards that have been incorporated into the clinical site where children will be studied.

(c) Information on the study's funding source and on liability coverage if the sponsor is not VA.

(d) A description of the relevance to Veterans' health of both the study and the inclusion of children in the study.

(e) If the sponsor of the research is not VA, the sponsor has procured appropriate liability insurance.

(2) If the study involves biological specimens or data collected from children, in addition to the preceding requirements, the following must be submitted:

(a) A discussion of how the biological specimens or data were, or will be, obtained and under what consents or authorization.
(b) If the biological specimens or data were, or will be, collected for research purposes, the IRB approval, the informed consent form, and the HIPAA authorization for the research.
(c) If biological specimens or data were, or will be, collected from an international site, approval by the medical facility Director for international research.
(d) Plans for future use of biological specimens or data.

The medical center Director will review the minutes of the IRB meeting approving the study. The IRB minutes need to reflect the discussion regarding level of risk, the informed consent and assent forms, the Investigators' qualifications to conduct research involving children, and any additional safeguards incorporated into the protocol.

1.6 Pregnant Women

This section applies to women who are pregnant at the time they are entered into a study. It does not preclude entering women of child bearing potential into research studies. Research involving pregnant women may be conducted at the Durham VAHCS if the research is relevant to the health of Veterans.

Women who are known to be pregnant and/or their fetuses may be involved in research if all of the requirements of 45 CFR 46.204 are met including informed consent requirements and the following ethical and scientific criteria:

a) 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;
b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or fetus. If there is no such prospect of benefit, t hen the 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;
c) Any risk is the least possible for achieving the objectives of the research; and
d) The medical facility Director certifies that the medical facility has sufficient expertise in women's health to conduct the proposed research. Specifically, the Director must certify that the facility is able to respond to obstetric emergencies if

the research involves an intervention greater than minimal risk in pregnant women at the facility.

Unilateral exclusion of non-pregnant women of reproductive potential from research is not permitted by the IRB. However, when justified, this option may be considered by the IRB for women of childbearing potential.

1.7 Subjects Who Lack Decision-making Capacity

No individual who lacks decision-making capacity may participate in VA Research until the IRB has reviewed and approved that individual's, or that class of individuals' participation in a given study.

1.7.1 Determination of Capacity

When planning to enter subjects with impaired decision-making capacity, investigators must address in the protocol how they will determine when surrogate consent (i.e., a LAR) will be required. In general, the research staff must perform or obtain and document a clinical assessment of decision-making capacity for any subject suspected of lacking decision-making capacity. However, the IRB must review and approve the plan to ensure that it is appropriate given the population and setting of the research. Note: Individuals ruled incompetent by a court of law are considered to lack decision-making capacity.

For example, the investigator may choose this process in their protocol:

> An individual is presumed to have decision-making capacity unless it has been documented by a qualified practitioner in the individual's medical record in a signed and dated progress note that the individual lacks capacity to make the decision to participate in the proposed study (***NOTE:*** *The qualified practitioner may be a member of the research team),* or the individual has been ruled incompetent by a court of law.
>
> If there is any question as to whether or not a potential adult subject has decision-making capacity, and there is no documentation in the medical record that the individual lacks decision-making capacity, and the individual has not been ruled incompetent by a court of law, the Investigator must consult with a qualified practitioner (who may be a member of the research team) about the individual's decision-making capacity before proceeding with the informed consent process.

1.7.2 Temporary or Fluctuating Lack of Decision-Making Capacity

Individuals, who because of a known condition, are at high risk for temporary (e.g., head trauma) or fluctuating (e.g., schizophrenia) lack of decision-making capacity must be evaluated by a qualified practitioner (who may be a member of the research team), to

determine the individual's ability to provide informed consent. This evaluation must be performed as described in the IRB-approved protocol. If the individual is deemed to lack decision-making capacity at the time of their participation in the study, a LAR must provide informed consent. If the subject regains decision-making capacity, the Investigator or designee must repeat the informed consent process with the subject, and obtain the subject's permission to continue with the study.

1.7.3 Criteria for Enrollment

Individuals who lack decision-making capacity may be enrolled in protocols if:

(1) The IRB determines that the proposed research entails:
  (a) No greater than minimal risk to the subject; or
  (b) Presents a greater probability of direct benefit to the subject than harm to the subject; or
  (c) Greater than minimal risk and no prospect of direct benefit to individual subjects, but is likely to yield generalizable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the subject's disorder or condition.

(2) The research cannot be performed solely with persons who possess decision-making capacity and the focus of the research is the disorder (e.g., Alzheimer's) leading to the individual's lack of decision-making capacity, whether or not the lack of decision-making itself is being evaluated (e.g., an individual who lacks decision-making capacity as the result of a stroke can participate in a study of cardiovascular effects of a stroke).

(3) The subject of the study is not directly related to the individual's lack of decision-making capacity, but the Investigator can make a compelling argument for including individuals who lack decision-making capacity in the study (e.g., transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in a nursing home where both individuals with, and those without, decision-making capacity are affected).

1.7.4 IRB Determination

The IRB may approve the inclusion of individuals who lack decision-making capacity in research studies on the basis of informed consent from LARs.

Before approving the study, the IRB must ensure the study includes appropriate procedures for respecting dissent; consider whether or not the study needs to include procedures for obtaining assent; and determine whether any additional safeguards need to be used (e.g., consent monitoring).

The IRB must document its deliberations and the criteria it used to approve inclusion of individuals who lack decision-making capacity in the IRB minutes or IRB protocol file.

1.7.5 Additional Safeguards

Investigators must request IRB approval to use surrogate consent specific to the research study being reviewed.

The IRB membership must include at least one member who is an expert in the area of the research. Consideration may be given to adding another member who is a member of the population, a family member of such a person or a representative of an advocacy group for that population.

The IRB may utilize ad hoc members as necessary to ensure appropriate expertise. Research involving persons with impaired decision making capacity may only be approved when the following conditions apply:

- Only incompetent persons or persons with impaired decision making capacity are suitable as research subjects. Competent persons are not suitable for the proposed research. The Investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision making capacity as subjects. Incompetent persons or persons with impaired decision making capacity must not be subjects in research simply because they are readily available.

- 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.

- 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 guardian, must be given descriptions of both proposed research studies and the obligations of the person's representative. 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 the incompetent person's best interest.

The IRB must make a determination in writing of each of the criteria listed above. If these criteria are met, the IRB may approve the inclusion of incompetent subjects or subjects with impaired decision making capacity in research projects on the basis of informed consent from authorized representatives as follows:

- Under appropriate conditions, Investigators may obtain consent from the legally authorized representative of a subject (surrogate consent).

- This policy is designed to protect human subjects from exploitation and harm and, at the same time, make it possible to conduct essential research on problems that are unique to persons who are incompetent, or who have an impaired decision making capacity (e.g., a study of treatment options for comatose persons can only be done with incompetent subjects).

- The State of North Carolina does not have a statue addressing the capacity of adults to consent to procedures solely for research purposes. According to VHA guidance and the Durham VAHCS IRB such consent may be obtained from:

    1. A health care agent appointed by the person in a DPAHC or similar document;
    2. Legal guardian or special guardian;
    3. Next of kin in the following order of priority:
        - spouse
        - adult child (18 years or older)
        - parent
        - adult sibling (18 years or older)
        - grandparent
        - adult grandchild (18 years or older)
    4. A close friend.

    Note: *the preceding list contains the only surrogate entities who are allowed to provide consent for research purposes.*

Such 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 medical record in a signed and dated progress note. The determination must be made in accordance with the following requirements or as established by a legal determination.

a) The practitioner, in consultation with the chief of service or COS, 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.
b) 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) Disclosures required to be made to the subject by the Investigator must be made to the subject's surrogate.
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.

1.8 Other Vulnerable Groups

Although federal regulations list vulnerable groups, other vulnerable groups may include employees, terminally ill patients, and the very elderly. The IRB will determine special protections for these groups on a case-by-case basis, taking into account the risks and benefits and other protections afforded by institutional policies and state and federal law.

The issues with respect to employees as research subjects are coercion or undue influence, and confidentiality. Employee research programs raise the possibility that the decision will affect performance evaluations or job advancement. It may also be difficult to maintain the confidentiality of personal medical information or research data when the subjects are also employees. The VA has strict policy regarding compensation of employees. The Investigator is responsible for following those policies.

1.9 Subjects in "Treatment IND" studies

Informed consent is especially important in treatment use situations because the subjects are desperately ill and particularly vulnerable. They will be receiving medications that have not been proven either safe or effective, in a clinical setting. Both the setting and their desperation may work against their ability to make an informed assessment of the risk involved. IRBs must ensure that potential subjects are fully aware of the risks involved in participation.

IRBs should also pay particular attention to Treatment INDs in which the subjects will be charged for the cost of the drugs. The question here is one of equitable selection and the involvement in research of vulnerable populations, particularly economically disadvantaged persons [see 21 CFR 56.111(a)(3)]. If subjects will be charged for use of the test article, economically disadvantaged persons will likely be excluded from participation. The stated purpose of the Treatment IND exemption is to facilitate the availability of promising new drugs to desperately ill patients while obtaining additional data on the drug's safety and effectiveness. Charging for participation may preclude economically disadvantaged persons as a class from receiving access to test articles. IRBs will need to balance this interest against the possibility that unless the Sponsor can charge for the drug, it will not be available for treatment use until it receives full FDA approval.

2. Scope

These policies and procedures apply to all research submitted to the IRB.

3. Responsibility

ACOS/R&D, Research Compliance Officer (or equivalent) is responsible for maintaining up-to-date review tools for review of research pertaining to vulnerable groups based on new and evolving applicable regulations and guidelines.

IRB Chairperson (or designee) is responsible for ensuring the IRB members are well versed in new and evolving regulations and guidelines pertaining to vulnerable populations, for selecting primary reviewers with appropriate expertise to conduct the reviews of such research, and for securing appropriate consulting expertise as needed for selected reviews.

IRB Reviewer is responsible for conducting appropriate review of research planned for vulnerable populations, including an assessment of potential for coercion, in consultation with any appropriate experts and resources.

SC 502: CATEGORIES OF RESEARCH

1. Policy

The categories of research defined in these policies involve either methodologies that might require additional considerations or for which there are federally mandated determinations that IRBs are required to make and document. These categories of research include, but are not limited to:

- Clinical research involving investigational drugs
- Clinical research involving devices
- Genetic research
- Emergency use of an investigational article
- Medical records and chart review
- Residual body fluids, tissues and recognizable body parts
- Collaborative Research
- Certificates of Confidentiality

1.1 Clinical Research Involving Investigational Drugs

Investigational new drug means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms “investigational drug” and “investigational new drug” are deemed to be synonymous (21 CFR 312.3).

All protocols that involve the use of an investigational drug, biologic product, or test article (FDA and VA definition) must receive IRB and R&D approval. The IRB will evaluate whether or not a clinical investigation must be conducted under an investigation new drug application (IND) subject to 21 CFR 312 and will determine, when applicable, that a valid IND is present before approving the research.

Investigators are responsible for supplying sufficient to the IRB to make the determination.

When an Investigator holds an IND for investigational uses of test articles, the Investigator assumes all the responsibility of a sponsor of the clinical investigation under the IND and has responsibilities that can be found in 21 CFR 312, in addition to those listed in this document. The Investigator’s status is one of sponsor-Investigator (21 CFR 312.3). Sponsor responsibilities may be delegated to another person only by written agreement. Regulatory monitoring for clinical investigations performed by an Investigator holding an IND will include monitoring sponsor responsibilities. FDA letters to the sponsor-Investigator typically contain guidance on the Investigator’s responsibilities to the FDA. The Investigator must provide a plan to the IRB for fulfilling these responsibilities.

When an Investigator assumes the role and responsibilities of a sponsor-Investigator, the IRB Chair in conjunction with the Research Compliance Officer will evaluate the Investigator's knowledge (and educate if necessary) regarding FDA regulatory requirements according to 21 CFR 312. The following is an example of responsibilities to be addressed:

- Monitoring responsibilities
- Adverse event reporting
- Maintenance of adequate records of essential documents and Clinical Trial Materials
- Annual reports

Investigator responsibilities for studies with investigational drugs may be found in SOP RI 801.

1.1.1 IND Exemptions

The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from IND requirements if all the following apply:

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

In vitro diagnostic products (blood grouping serum, reagent blood cells, and anti-human globulin) are exempt from IND requirements provided that the clinical investigation involving the in vitro diagnostic biological product is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and it is shipped in compliance with 21 CFR 312.160.

A drug intended solely for tests in vitro or in laboratory research animals is exempt if shipped in accordance with 312.160.

A clinical investigation involving use of a placebo is exempt if the investigation does not otherwise require submission of an IND.
For more in-depth information regarding IND exemptions, see 21 CFR 312.2.

1.1.2 Research Service Responsibilities

The Research Service will work with the Pharmacy Service as needed to ensure that Pharmacy receives appropriate reimbursement for required supplies and services as described in VHA Handbook 1108.04.

1.1.3 Pharmacy Service/ Investigational Pharmacist Responsibilities

The Research Pharmacist is responsible for the receipt, storage, security, labeling, dispensing, and disposition of all investigations drugs and supplies used in clinical investigations, and for ensuring that all other pharmacy duties are performed as outlined in local Pharmacy policies and VHA Handbook 1108.04.

Regardless of the source, all investigational and sponsor supplied drugs must be delivered to the Pharmacy Service or Research Service Investigational Pharmacy for receipt, storage, security, labeling, distribution, dispensing, and disposition.

Investigational drugs are not to be obtained from other facilities or PIs without an approved Letter of Understanding (LOU) and adherence to protocol procedures and FDA requirements. An LOU can exist between a university affiliate or a VA affiliate and the VA Medical facility (or a parent VA Medical facility and its affiliated satellite clinics). Detailed information as to how drugs are to be dispensed and accounted for must be clearly stated in the Investigational Drug LOU.

While not encouraged, the Pharmacy Service / Investigational Pharmacist has the authority to store investigational drugs outside of the pharmacy, provided that a Delegation of Custody document is in place per VHA Handbook 1108.04 and the Investigator complies with all dispensing and documentation requirements.

1.2 Clinical Research Involving Devices

Investigational device means a device, including a transitional device, that is the object of an investigation.

When research is conducted to determine the safety or effectiveness of a device, the IRB confirms that:

- The device fulfills the requirements for an abbreviated IDE.
    - The device is not a banned device.
    - The sponsor labels the device in accordance with 21 CFR 812.5.

  - The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval.
  - The sponsor ensures that each investigator participating in an investigation of the device obtains for each subject under the investigator's care, consent under 21 CFR 59 and documents it, unless documentation is waived.
  - The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations.

- The device fulfills one of the IDE exemption categories:
  - A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
  - A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.
  - A diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
    - Is noninvasive;
    - Does not require an invasive sampling procedure that presents significant risk;
    - Does not by design or intention introduce energy into a subject;
    - Is not used as a diagnostic procedure without confirmation of the diagnosis of another, medically established diagnostic product or procedure.
  - A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purposes of determining safety of effectiveness and does not put the subjects at risk.
  - A custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification [510(k)] submission to FDA. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. All clinical evaluations of investigational

devices, unless exempt (see 21 CFR 812.2 (c), must have an approved IDE before the study is initiated.

Significant risk device means an investigational device that:

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

A nonsignificant risk device is one that does not meet the definition for a significant risk.

The IRB will determine whether or not a clinical investigation must be conducted under an investigation device exemption (IDE) subject to 21 CFR 812 and will determine, when applicable, that a valid IDE is present before approving the research.
For studies involving investigational devices that are not exempt from the IDE requirements, do not have an IDE, and for which the sponsor claims is not a significant risk device, the IRB will make an assessment of whether the device is a significant risk device. Investigators are responsible for supplying sufficient information to the IRB to make the determination. When a study claims to involve a non-significant risk device, the sponsor through the Investigator must supply the IRB with an explanation of its claim. The IRB must review the sponsor's justification for the NSR determination. The IRB will assess the risk status of the device according to the definition of significant risk device in FDA regulations. The IRB's device risk determination must be documented in the IRB meeting minutes.

If an Investigator submits an NSR device research protocol that is determined by the IRB to be a significant risk device study, the IRB will notify the Investigator and FDA in writing. No further action will be taken by the IRB on the research until the Sponsor or Investigator has provided adequate justification or met the requirements for an SR study described in 21 CFR 812 (Investigational Device Exemption regulations).
SR device studies must be conducted in accordance with the full IDE requirements (21 CFR Part 812). Pursuant to these regulations, an investigation may begin 30 days after FDA receives the application (unless FDA provides notification that the investigation may not begin), or after the FDA approves, by order, an IDE for the investigation (21 CFR 812.30). In addition, the Investigator must have approvals from the IRB and R&D committee. The FDA considers all SR studies to be greater than minimal risk, and therefore do not qualify for expedited review at initial review.

For SR device studies, the Investigator must provide the IRB with a copy of the FDA's approval of the IDE application.

NSR device studies do not require submission of an IDE application, but must be conducted in accordance with the "abbreviated requirements" of the IDE regulations (21 CFR 812.2(b)). NOTE: NSR devices may represent greater than minimal risk depending upon the research study.

Receipt, storage, security, and dispensing responsibilities of investigational devices must be addressed by the Investigator in the protocol at the time of submission and approved by the IRB. For all investigational device research approved by the Durham VAHCS, regulations found at 21 CFR 812.140 will apply.

Investigational devices must be appropriately managed to ensure they are not mixed with and/or mistaken for similar approved devices. It is difficult to provide a single storage mechanism for research devices as with investigational drugs. In some cases investigational devices must be maintained in sterile supply, autoclaved or otherwise processed for implantation or use. It may be necessary for some devices to be installed, provided in a variety of sizes, or custom ordered. Each Investigator shall maintain accurate, complete, and current records relating to their participation in an investigation (see SOP RI 801).

1.3 Humanitarian Use Device

A Humanitarian Use Device (HUD) is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4000 individuals in the U.S. per year (21 CFR 814.3(n)). ***NOTE:*** *If a physician uses a HUD as defined and described in FDA regulations, the physician must follow FDA regulations.*

1.4 Genetic Research

Genetic research may require special considerations.

1.4.1 Subjects of Genetic Research

At first consideration, much genetic research may appear to meet the criteria for expedited review. These include:

- Pedigree studies, which look for a pattern of inheritance of a gene;
- Positional cloning studies, which are conducted to identify particular genes;
- Diagnostic studies, which gather samples to develop techniques to determine the presence of specific DNA mutations.

However, these studies may create a vulnerable population in that subjects' autonomy may be compromised. Therefore the full IRB must review these studies to answer the following questions: Will the samples be made anonymous to maintain confidentiality? If not, to what extent will the results remain confidential; and who will have access to them? Will the samples be used for any additional studies not made explicit at the time of donation, or will the samples be destroyed after specified, one-time use? Will the donor be informed of any and all results obtained from his or her DNA? Will the donor be informed of the results of the entire study? Will family members be implicated in the studies without consent?

Gene therapy research (administration of recombinant vectors), which is carried out to develop treatments for genetic diseases at the DNA level, presents obvious and not so obvious questions, including – considerations of delivery methods, target population, required follow-up. Such protocols might require use of external consultants to provide independent guidance to the IRB. If the project involves gene therapy to human subjects for other than clinical purposes, the study must be reviewed and approved by the National Institutes of Health Recombinant DNA Advisory Committee prior to IRB approval. Monitoring must be adequate, and a DSMB will be required.
Because there is still little regulatory guidance and relatively few ethical precedents, genetic research will require close scrutiny, and the possible input of experts in this area.

1.5 Prospective Research in Emergency Settings (21 CFR 50.24)

The Durham VAHCS does not conduct planned emergency research.

1.6 Emergency Use of Test Articles

An investigational test article may be used in an emergency prior to IRB review, provided that the patient is 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.

Such emergency use is reported to the IRB within 5 working days, and any subsequent use of the test article is subject to prior IRB review.

When an Investigator conducts an emergency use of a test article in a life-threatening situation without prior IRB review, the activity is research under FDA regulations and the patient is a subject under FDA regulations. FDA may require data from an emergency use of a test article in a life-threatening situation to be reported in a marketing application.

Whenever possible, Investigators are to contact the IRB in advance of the emergency use of a test article.

When an Investigator must proceed without prior IRB approval informed consent shall be considered feasible except as follows: in certain emergency situations where the Investigator has adequately documented the necessary exception under the guidelines described in 21 CFR 50.23(b). The Investigator must use the Criteria for Emergency Use of a Test Article to follow and document the regulatory requirements. The Investigator must submit documentation to the IRB for review within 5 working days after emergency use of the test article. In review of the documentation, the IRB will ensure that the Investigator and a physician not otherwise participating in the clinical investigation have adequately certified the following in writing prior to use of the test article:

- The research was subject to VA regulations regarding human subject protections.
- The human subject was confronted by a life-threatening situation necessitating the use of the test article.
- Informed consent could not be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.
- Time was not sufficient to obtain consent from the subject's legal representative.
- There was no alternative method of approved or generally recognized therapy available that provided an equal or greater likelihood of saving the life of the subject.

If immediate use of the test article is, in the Investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the required independent physician’s determination prior to administering the test article, the determinations of the Investigator shall be made and, within 5 days after the use of the test article, be reviewed and evaluated in writing by a physician not otherwise participating in the clinical investigation. In this event, a copy of the independent review must be submitted to the IRB within 5 working days after the use of the test article. This documentation along with the Criteria for Emergency Use of a Test Article form must be submitted to IRB within 5 working days after the use of the test article.

The IRB will review the documentation and determine by using/reviewing Criteria for Emergency Use of a Test Article form that the circumstances met regulatory criteria. The Investigator will be notified of the IRB’s decision in writing and informed that subsequent uses are subject to prior IRB approval.

If the IRB determines that the criteria for Emergency Use of a Test Article were not met, the Investigator will be notified in writing and informed the use is subject to noncompliance.

1.6.1 Use of data generated prior to IRB approval

Whenever emergency care is initiated without prior IRB review and approval, the patient may *not* be considered to be a research subject. DHHS regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval.

For DHHS-supported or conducted research, the physician may, without prior IRB approval, treat the patient/subject using a test article (if the situation meets the FDA requirements), but the subject may not be considered a research subject and data derived from use of the test article may not be used in the study.

1.7 Medical Records and Chart Review

Studies involving the use of existing public or privately held records only may qualify for exempt status or expedited review. However, if the nature of the research could put subjects' confidentiality at risk, the study will be reviewed by the full IRB. Studies that involve only chart and record review can sometimes pose significant risk to patients.

The most common breach of confidentiality is exposure of possibly embarrassing information without the knowledge or consent of the patient. Such studies may also lead to recruitment of patients into future non-therapeutic studies in a manner which may provoke the patient to ask how his/her record was revealed to someone not part of his/her therapeutic team. The present policy is to require IRB review of studies involving chart review or data collection and analysis.

If identifiers were to be recorded, the research would require IRB review to ensure that, among other things, procedures for protecting privacy and confidentiality are adequate. Furthermore, the Investigator studying cancer risk factors may propose to go on to contact the subjects (if still living) or family members (if the subject is deceased) to gather additional information, which may or may not be subject to the federal regulations.

1.8 Residual Body Fluids, Tissues and Recognizable Body Parts

Body Fluids & Tissues: Research on existing specimens ("on the shelf" or frozen) without identifying information (e.g., no names, initials, hospital number, etc.) may be submitted to the IRB for expedited review, to include a short description of the research and where the tissue is coming from. Research on existing specimens may be eligible for exemption from IRB review. In order to meet this requirement all specimens used in the research must be in existence prior to the initiation of the research. Investigators cannot self-exempt their research; the information must be submitted to the Research Office. At the Durham VAHCS the IRB chair or designee determines whether research meets the exemption criteria.

1.9 Collaborative Research

This addresses collaborations between VA and non-VA investigators. Collaboration is encouraged when VA investigators have a substantive role in the design, conduct, and/or analysis of the research. VA may also serve as a Coordinating Center for collaborative studies. ***NOTE:*** *Collaborative studies do not include studies conducted under a CRADA with pharmaceutical companies or other for-profit entities.*

1.9.1 IRB of Record Approval

Each institution is responsible for safeguarding the rights and welfare of human subjects and providing oversight of the research activities conducted at that institution.
(1) Each collaborating institution engaged in human subjects research must obtain approval from its IRB of Record and hold a FWA or another assurance acceptable to VA, e.g. DoD assurance.

(2) VA investigators must submit a protocol or other documentation to their VA IRB of Record that delineates which research activities will be conducted by VA.
(3) Each institution engaged in the collaborative research must use the informed consent document and HIPAA authorization required by their respective institutional policies for subjects recruited from that institution, or procedures requiring participation of the subject at that institution. The informed consent document may contain information on the project as a whole as long as the document clearly describes which procedures will be performed at VA and which will be performed at other institutions.

(a) The VA informed consent document must clearly state when procedures mentioned at other institutions are part of the VA's portion of the study.
(b) The informed consent document and HIPAA authorization must be consistent and include information describing the following:

1. PHI to be collected and/or used by the VA research team;
2. PHI to be disclosed to the other institutions; and
3. Purpose for which the PHI may be used.

(c) **Waivers.** PHI obtained in research for which the IRB of Record has waived the requirements to obtain a HIPAA authorization and a signed informed consent document may not be disclosed outside VA unless the VA facility Privacy Officer ensures and documents VA's authority to disclose the PHI to another institution. A waiver of HIPAA authorization is not sufficient to fulfill the requirements of other applicable privacy regulations such as the Privacy Act of 1974 (5 U.S.C. 552a).

1.9.2 Research Data

The protocol, addendum, and/or IRB of Record application must describe the data to be disclosed to collaborators, the entity(ies) to which the data are to be disclosed, and how

the data are to be transmitted. This includes data from individual subjects as well as other data developed during the research such as the analytic data and the aggregate data.

(1) Each VA facility must retain a complete record of all data obtained during the VA portion of the research in accordance with privacy requirements, the Federal Records Act, and VHA Records Control Schedule (RCS) 10-1.
(2) All disclosures and data transmission must meet privacy and security requirements per VA Directive 6500, VA Handbook 6500, and VHA Directive 1605.01.

1.9.3 Written Agreements

Collaborative research involving non-VA institutions may not be undertaken without a signed written agreement (e.g., a CRADA or a Data Use Agreement (DUA)) that addresses such issues as the responsibilities of each party, the ownership of the data, and the reuse of the data for other research. ***NOTE:*** *Any reuse must be consistent with the protocol, the informed consent document, and the HIPAA authorization.*

1.10 Certificates of Confidentiality

Several HHS operating agencies issue Certificates of Confidentiality to protect research subjects. Generally, any research project that collects personally identifiable, sensitive information and that has been approved by an IRB operating under either an approved FWA issued by the OHRP or the approval of the FDA is eligible for a Certificate of Confidentiality. Sensitive information for purposes of a Certificate of Confidentiality includes (but is not limited to) information relating to sexual attitudes, preferences, or practices; information relating to the use of alcohol, drugs, or other addictive products; information pertaining to illegal conduct; information that, if released, might be damaging to an individual's financial standing, employability, or reputation within the community or might lead to social stigmatization or discrimination; information pertaining to an individual's psychological well-being or mental health; and genetic information or tissue samples.

Some types of research projects that are eligible for a Certificate of Confidentiality include:

(1) Research on HIV, Acquired Immune Deficiency Syndrome, and other sexually transmitted diseases;
(2) Studies that collect information on sexual attitudes, preferences, or practices;
(3) Studies on the use of alcohol, drugs, or other addictive products;
(4) Studies that collect information on illegal conduct;
(5) Studies that gather information that if released could be damaging to a participant's financial standing, employability, or reputation within the community;

(6) Research involving information that might lead to social stigmatization or discrimination if it were disclosed;
(7) Research on participants' psychological well-being or mental health;
(8) Genetic studies, including those that collect and store biological samples for future use; and
(9) Research on behavioral interventions and epidemiologic studies.

Investigators and IRBs are urged to consider the use of Certificates of Confidentiality when appropriate.

When VA conducts a study that is protected by a Certificate of Confidentiality, the following health record documentation provisions apply:

(1) For studies that do not involve a medical intervention (e.g., observational studies, including interview and questionnaire studies), no annotation may be made in the health record.
(2) For studies that involve a medical intervention, a progress note entry should indicate that an individual has been enrolled in a research study, any details that would affect the subject's clinical care, and the name and contact information for the investigator conducting the study. Subjects' informed consent forms and HIPAA authorization documents are not to be included in the health record.

Investigators should work with the research office in their facility to assure that when Veterans are enrolled in a study protected by a Certificate of Confidentiality, they are not simultaneously enrolled in other interventional studies unless it is absolutely clear that this enrollment does not raise safety issues.

2. Scope

These policies and procedures apply to all research submitted to the IRB.

3. Responsibility

IRB Program Administrator is responsible for maintaining up-to-date review tools for review of research pertaining to these categories based on new and evolving applicable regulations and guidelines.

IRB Chairperson (or designee) is responsible for ensuring the IRB members are well versed in new and evolving regulations and guidelines pertaining to these categories, for selecting primary reviewers with appropriate expertise to conduct the reviews of such research, and for securing appropriate consulting expertise as needed for selected reviews.

IRB Reviewer is responsible for conducting appropriate review of research planned for these categories in consultation with any appropriate experts and resources.

SC 503: ENGAGEMENT IN RESEARCH

1. Policy

The IRB will determine whether participating sites are considered engaged in research based on OHRP guidance.

1.1 Engagement

In general, the Durham VAHCS or an affiliated CBOC is considered "engaged" in a particular non-exempt human subjects research study when an individual with a VA appointment (including full and part-time employees, WOC employees, and employees under the IPA of 1970) at that facility obtains for the purposes of the research study:

(1) Data about the subjects of the research through intervention or interaction with them;
(2) Identifiable private information about the subjects of the research; or
(3) The informed consent of human subjects for the research.

When a VA facility is engaged in human subject research, it must:
(1) Hold an FWA;
(2) Have a VA PI or LSI for that study; and
(3) Have the facility's IRB of record approve the study.

1.2 Non-Engagement

If a VA facility is not engaged in any human research then the VA facility does not need to have an FWA.

If a VA facility is not engaged in research for the purposes of an individual study, then its IRB of record does not need to approve that study.

If a VA facility is not engaged in research for the purposes of a given study, it has no jurisdiction over that study, except the facility Director may determine that the study cannot be conducted on its premises.

NOTE: *See OHRP Guidance on Engagement of Institutions in Human Subjects Research, October 16, 2008, for examples and additional guidance.*

2. Scope

This applies to all research conducted at the Durham VAHCS.

3. Responsibility

The Durham VAHCS IRB is responsible for determining engagement in research.

Investigators must provide the IRB with enough information for the IRB to make this determination.

SC 504: MULTI-SITE STUDIES

1. Policy

If conducting human research studies involving more than one engaged institution, each institution is responsible for safeguarding the rights and welfare of human subjects entered at its site, and for complying with all applicable local, VA, and other Federal requirements.

1.1 Investigator Responsibilities

1.1.1 Lead Investigator of a VA Multi-Site Study

In addition to the requirements in SOP RI 801, Investigators are required to submit to the IRB certain communications when s/he is the lead Investigator of a multi-site study and responsible for the overall conduct of the study or provides study-wide services such as data coordination. The initial protocol submission must include sufficient information for the IRB to determine that the management of information relevant to the protection of subjects is adequate. The Investigator will submit the following:

a. Information that indicates the research will be conducted at multiple sites;
b. A thorough and clear description of the type of activities to conducted at each site;
c. A description of reporting requirements of serious adverse events, unanticipated problems, amendment/modifications for the other sites;
d. All IRB approvals and IRB-approved informed consent forms (when available, if applicable) from other sites before the study is implemented at that site;
e. A method for ensuring that all engaged participating sites have the most current version of the protocol, the most current version of the informed consent form, and the most current version of the HIPAA authorization.
f. A method for notifying the Director of any facility deemed by the PI's IRB of record not to be engaged in the research, but on whose premises research activities will take place, before initiating the study (e.g., the PI conducts a survey of employees at a facility that is not engaged in the research). The facility Director has the authority to disapprove the conduct of these research activities on that facility's premises.
g. A method for confirming that all amendments and modifications to the protocol, the informed consent form, and the HIPAA authorization have been communicated to engaged participating sites, and that all required local facility approvals (including approval by the local facility's IRB of record) have been obtained before the amendment or modification is implemented.
h. A method for assuring that all engaged participating sites will safeguard VA data as required by VA information security policies.

i. A method for communicating to engaged participating sites SAEs that have the potential to affect implementation of the study.
j. A method of communicating regularly with engaged participating sites about study events and interim results (if appropriate).
k. A method for ensuring that all LSIs conduct the study appropriately.
l. A method to ensure all non-compliance with the study protocol or applicable requirements is reported in accordance with VHA Handbook 1058.01.
m. Indication in the annual progress report that continuing review is being obtained and maintained at all sites.
n. A method for notifying local facility directors and LSIs when a multi-site study reaches the point that it no longer requires engagement of the local facility (e.g., all subsequent follow-up of subjects will be performed by the PI from another facility).

1.1.2 Local Site Investigator (LSI) for a Multi-Site Study

When the Investigator is a LSI for a multi-site study (whether the LSI is also a PI or solely a Local Site Investigator), the LSI must:

a. Conduct the study according to the most recently approved version of the protocol, the most recently approved version of the informed consent form, the most recently approved version of the HIPAA authorization, and all applicable local, VA and other Federal requirements;

b. Ensure that all amendments and modifications to the protocol and the informed consent form are submitted to and approved by the local IRB of record prior to initiating any changes;

c. Report any unanticipated internal or local SAEs, whether related or unrelated to the research, in accordance with VHA Handbook 1058.01;

d. Report study events and interim results (if available) to the local IRB of record as required by local IRB policies; and

e. Oversee all aspects of the study at their local site.

1.1.3 Durham VAHCS Researchers Conducting Research at Remote Sites

When Durham researchers are approved by remote IRBs to conduct research at remote sites, the PI must submit a copy of each remote site's IRB and R&D approval letters to the Durham IRB prior to engagement or research activities at that site.

1.2 Durham VAHCS Responsibilities for Multi-Site Research When the Durham's Investigator is the Multi-Site Study PI for All Participating Facilities and the VA Central IRB is Not Being Used

In addition to other IRB responsibilities mentioned in this document, when the VA facility's Investigator is the multi-site study PI or study sponsor for all participating facilities, and VA Central IRB is not being used, the PI's or study sponsor's local VA facility's IRB of record is responsible for:

(1) When a participating site is added to the study, determining:

(a) Whether or not that site will be engaged in human subjects research.

(b) If the site will be engaged in research, then reviewing and confirming that it has an active FWA and has provided documentation of all relevant approvals, including approval of its IRB of record.

(2) Approving the study-wide protocol and sample informed consent document to be provided to each LSI at engaged facilities.

(3) Ensuring the study-wide protocol contains a mechanism for ensuring that any differences in the protocol or informed consent at engaged local participating sites are justified by the LSI, and that they are approved by the PI before being implemented.

(4) Ensuring there are clear AE reporting requirements, a data monitoring committee if applicable (or other reliable monitoring mechanism) with clear procedures and requirements, and a clearly defined feedback loop to the PI's or study sponsor's IRB.

(5) Reviewing the PI's plan for communicating appropriate critical information (e.g., reports of data and safety monitoring) to engaged participating sites.

(6) Ensuring, when relevant, confidentiality and information security requirements are met for information storage at and transmission to statistical or coordinating centers.

(7) Reviewing reports from applicable DMCs.

For research subject to Department of Defense (DoD) regulations: when conducting multi-site research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.

1.3 VA Central Institutional Review Board (CIRB) Studies

A Memorandum of Understanding (MOU) is in place between the Durham VAHCS and the VHA Central Office Institutional Review Board (CIRB) for the initial and continuing review, as well as review of amendments, monitoring, reporting, and other relevant requirements, for select ORD-funded multi-site research projects involving human subjects. As per the MOU, both institutions will adhere to 38 CFR 16 and 17, 45 CFR 46 Subpart A, and 21 CFR 50 and 56, as well as other pertinent VA and federal requirements applicable to human subject research.

The VA CIRB has been added to Durham VAHCS's FWA as an IRB of record for our facility.

1.3.1 VA CIRB Review and Submission Procedures

A. Principal Investigator / Study Chair Application:
1. After receiving notice from the VA CIRB administrator that the project is eligible to be reviewed by the VA CIRB, the PI/SC completes the New Project Application, VA CIRB Form 104.

2. The PI/SC submits the New Project Application (VA CIRB Form 108) and applicable supplemental documents to the Local Site Liaison. The Local Site Liaison obtains the ACOS/R&D signature on the application. The PI/SC is responsible for submitting the New Project Application to VA CIRB.

3.The PI/SC application is reviewed by VA CIRB at convened meeting or via expedited review. The PI/SC is responsible for maintaining all correspondence with VA CIRB.

4. When the PI/SC New Project Application has received approval, the local sites identified on the application are sent a copy of the approved application packet. The PI/SC, local site investigators, and Site Designee have 15 calendar days to provide comments or suggestions to the VA CIRB about the initial review determinations. The VA CIRB will review all comments from local sites and will make changes as applicable.

5. When the PI/SC has received full approval and the comments period has ended, review of the local site investigator applications will begin.

6. The PI/SC CIRB approved initial review packet, *Application for Initial Review of Research—VA CIRB Project*, and other local forms (as applicable) will be submitted to the R&D Committee, if the PI/SC resides at the DVAHCS. If applicable, review and approval by any other relevant local committees (Radiation Safety Committee, Sub-Committee on Research Safety (SRS)) will occur in accordance with local policy. If DVAHCS PI/SC is also serving as a Local Site Investigator (LSI), the approved LSI

initial review application will be included in the submission to relevant local subcommittees and to the R&D Committee after PI/SC and LSI approval by VA CIRB has been secured.

7. Once the R&D Committee approves the study, the official notification of approval will be signed by the ACOS/R&D and sent to the LSI. The LSI is responsible for sending all correspondence from the R&DC or ACOS/R&D to VA CIRB, and other entities as applicable. ***Note: The study cannot start until the LSI has received the approval letter from both the CIRB and Durham R&D Committee.***

8. A copy of the VA CIRB minutes where the PI/SC application was reviewed and approved will be sent to the Local Site Liaison and will be reviewed by the R&DC at the next scheduled committee meeting.

B. Local Site Investigator Application:

1. Once the PI/SC initial review application is approved, the LSI is instructed to prepare the Local Site Investigator Application (VA CIRB Form 104).

2. The DVAHCS LSI submits the LSI Application and applicable supplemental documents to the Local Site Liaison. The Local Site Liaison obtains the ACOS/R&D signature on the Local ACOS / R&D Review Supplement (VA CIRB Form 102). The LSI is responsible for submitting all documents to VA CIRB, via the PI/SC.

3. Once the application package is reviewed by CIRB, CIRB sends the LSI notification requiring they address stipulations, if applicable. This process includes making sure the local site consent form, as well as other submission documents, address local site criteria. The LSI has 30 calendar days to address initial review considerations. This response will be sent to the CIRB for further review.

4. Once the LSI initial review application is reviewed and approved by VA CIRB, the DVAHCS LSI will submit the CIRB approved LSI application packet, *Application for Initial Review of Research—VA CIRB Project*, and other local forms (as applicable) to the R&D Committee. If applicable, review and approval by any other relevant local committees (Radiation Safety Committee, Sub-Committee on Research Safety (SRS)) will occur in accordance with local policy. *Note: If the DVAHCS LSI is also serving as the PI/SC, the CIRB approved PI/SC initial review packet must also be submitted to R&DC.*

5. Once the R&D Committee approves the study, the official notification of approval will be signed by the ACOS/R&D and sent to the LSI. The LSI is responsible for sending any correspondence from the R&DC or ACOS/R&D to VA CIRB, PI/SC site, and any other entities as applicable. ***Note: The study cannot start until the LSI has received the approval letter from both the CIRB and Durham R&D Committee.***

6. A copy of the VA CIRB minutes where the LSI application was reviewed and approved will be sent to the Local Site Liaison and will be reviewed by the R&DC at the next scheduled committee meeting.

1.3.2 Durham Local Site Investigator (LSI) Responsibilities

The Durham LSI must comply with all CIRB Standard Operating Procedures (SOPs) and all responsibilities outlined in the Memorandum of Understanding (MOU) between the VA CIRB, DVAHCS, and NPC.

The Durham LSI must report all complaints, unanticipated problems involving risks to subjects or others, serious adverse events, suspension and/or termination of research, research impropriety, misconduct or restriction of any research team member to the VA CIRB.

The Durham LSI must follow the VA CIRB approved protocol and only use VA CIRB approved consent forms, HIPAA authorizations, advertisements, patient materials, etc., and not independently modify any VA CIRB-approved study except where necessary to eliminate apparent immediate harm to subjects (if this occurs, notify the CIRB of such actions within 5 working days; the R&DC committee must also be notified).

Continuing review of the study will be administered by the VA CIRB, not the Durham VAHCS IRB. The Durham LSI will submit the VA CIRB approved Local Site Investigator Continuing Review Application packet to the R&DC. If the DVAMC investigator serves as both the Principal Investigator/Study Chair (PI/SC) and the LSI for a multisite project, both the LSI and PI/SC continuing review applications and approval documents will be submitted to R&DC. The ACOS/R&D will notify the LSI, in writing, when the project has received continuing review approval by the R&DC and applicable subcommittees.

The Durham LSI will submit the VA CIRB approved Local Site Participant Closure report to R&DC. The LSI will be notified in writing when the protocol has been closed by the R&DC. R&DC cannot close a study until the study has been appropriately closed by VA CIRB.

The Durham LSI must ensure that all correspondence (i.e., amendments, protocol deviations, continuing reviews, etc.) from CIRB is maintained in the investigator files.

The Durham LSI must ensure that all study staff have all required training, scopes of practice, and credentialing and privileging to conduct research at the Durham VAHCS. The Durham LSI must notify CIRB and the DVAHCS Research Office of any changes in the local study team.

1.3.3 Durham VAHCS Responsibilities

The Durham VAHCS R&D Committee is responsible for conducting a local initial review for CIRB-approved studies. Studies under the purview of the VA CIRB may not be initiated locally until R&DC approval and all relevant local sub-committee approvals have been secured. For more details, please see the R & D Committee Standard Operating Procedures.

CIRB approved amendments, notifications, modifications, or updates to studies under the purview of VA CIRB do not require review by R&DC, unless requested by the RCO, VA CIRB, or ACOS/R&D. The local site liaison is notified by VA CIRB when approved study documents are available on SharePoint site. Copies of all approved documents will be stored in the Research Office in the electronic protocol file and accessible to R&DC, local RCO(s), and ACOS/R&D.

The Durham VAHCS will retain ultimate responsibility for oversight of the Human Research Protection Program, including that all research approved or determined exempt by the CIRB is submitted to the Durham R&D Committee for review; safeguarding the rights and welfare of human subjects of all research approved by the R&D Committee; and maintaining a culture of compliance with all VA and other federal requirements.

Responsibilities of the Durham VAHCS can be found in the MOU. Specifically, Durham VAHCS will:

- Agree not to independently modify any CIRB-approved study except where necessary to eliminate apparent immediate harm to subjects.
- Notify CIRB immediately of potential research impropriety, misconduct, suspension, debarment, or restriction of any local research team member associated with a CIRB-approved study.
- Provide CIRB access to the research subjects' clinical records and/or case files if required as part of any CIRB oversight or monitoring activity.
- Participate in the annual review of the CIRB, including an evaluation of the CIRB's composition and operation.
- Conduct routine compliance audits and monitoring. Note: Durham RCOs will perform 100% informed consent audits annually and a regulatory audit triennially (at a minimum). These results will be provided to the Durham R&D Committee and the Investigator; the Investigator must forward the audit report to the CIRB per CIRB requirements.
- Maintain a file for each CIRB approved project.

1.3.4 CIRB Responsibilities

Responsibilities and required actions of the CIRB can be found in the MOU.

2. Scope

This applies to all multi-site research conducted at the Durham VAHCS or by Durham VAHCS researchers.

3. Responsibility

The Facility Director for a VA facility using the VA Central IRB as an IRB of record is responsible for signing and adhering to the MOU between VHA Central Office and the local VA facility delineating the respective roles and responsibilities of each organization, and delegating authority to an individual from the local VA facility to comment and respond to VA Central IRB review and serve as a liaison**.**

SC 505: INTERNATIONAL RESEARCH

1. Policy

All individuals who participate as subjects in research at international sites must be provided appropriate protections that are in accord with those given to research subjects within the U.S., as well as protections considered appropriate by local authority and custom at the international site (38 CFR 16.101(g)).

VA international research is defined as any VA-approved research conducted at international sites (not within the U.S., its territories, or Commonwealths); any VA-approved research using either human biological specimens (identified, de-identified, or coded) or human data (identified, de-identified, or coded) originating from international sites; or any VA-approved research that entails sending such specimens or data out of the U.S. This definition applies regardless of the funding source (funded or unfunded) and to research conducted through any mechanism of support including MOUs, CRADAs, grants, contracts, or other agreements. ***NOTE:*** *Research conducted at US military bases, ships, or embassies is not considered international research.*

Sending specimens or data to individuals with VA appointments at international sites (e.g., a WOC appointment, a VA Investigator on sabbatical at an international site) is considered international research. Remote use of data that is maintained on VA computers within the US or Puerto Rico and accessed via a secure connection is not considered international research.

1.1 Multi-Site Trials

International research includes multi-site trials involving non-US sites where:

(1) VA is the study sponsor;
(2) a VA investigator is the overall study-wide PI;
(3) VA holds the Investigational New Drug (IND); or
(4) the VA manages the data collection and the data analyses

NOTE*: International research does not include studies in which VA is only one of multiple participating sites where the overall study-wide PI is not a VA investigator.*

1.2 IRB and Facility Director Permission

Before approving international research involving human subjects research, the IRB must ensure that human subjects outside of the US who participate in research projects in which VA is a collaborator receive equivalent protections as research participants inside the US.

All international research must be approved explicitly in a document signed by the VA medical facility Director, except for Cooperative Studies Program activities which must be approved by the CRADO. The Investigator should work with the Research Office to ensure medical facility Director approval.

1.3 FWA and Approval

All international sites must hold an international FWA and the research must be approved by the IRB or Research Ethics Board of the participating site(s) that are listed on the international FWA.

1.4 Department of Defense (DoD) International Research Requirements

For DoD-funded studies, the facility or Investigator must have permission to conduct research outside of the United States by certification or local ethics review; therefore, the Investigator must provide the Durham VAHCS IRB with documentation that s/he has relevant permission to conduct the research (i.e., via an IRB or Ethics Committee (EC) approval letter, or some other formal documentation of approval by relevant authorities).

In addition, the Investigator must follow all local laws, regulations, customs, or practices of the host country; therefore, the Investigator must provide the Durham VAHCS IRB with formal documentation of training in local research laws, regulations, customs, or practices. This requirement may be satisfied by taking the host country's local IRB or EC required research training and providing documentation of that training.

2. Scope

This applies to all research and Investigators at the Durham VAHCS.

3. Responsibility

Facility Director's responsibilities: In addition to VA facility Director responsibilities delineated elsewhere in this document, the facility Director is responsible for approving the request for permission to conduct international research prior to its initiation by an Investigator at the facility.

PI responsibilities: In addition to the PI responsibilities delineated elsewhere in this document, the PI is responsible for obtaining approval from the facility Director in writing before initiating an international research study, and conducting research in compliance with this document and all other applicable VA and other Federal requirements including those for protecting human subjects, tissue banking, use of databases, federal criminal laws, and the Standards of Ethical Conduct for Employees of the Executive Branch.

SC 506: VA DATABASE AND RESEARCH ACCESS FORM REQUESTS FOR RESEARCH PROTOCOLS

1 Policy

This policy defines procedures for review and approval of requests using VA Form 9957 "Access Form" when requesting access to VA databases for research purposes. This policy includes instruction for form completion and for proper routing of the form through the Research Office for form completion.

2 Scope

This policy applies to any request that requires the use of VA Form 9957 for either an active or planned research protocol. This policy does not apply to request for database access for clinical or quality improvement purposes. This policy provides guidance to the investigative staff and the research administrative staff on proper processing of these requests.

2.1 Completion of Form 9957

1) The most recent version of VA Form 9957 must be used to request access to VA databases and related VA resources.

2) The form should be filled out according to the following instructions:
   - The form is completed by the individual requiring the access.
   - The form must be filled out and signed with a digital signature and dated.
   - Digital signatures are required. No forms will be accepted with ink signatures.
   - The individual requiring the access or receiving the data should indicate their current status of Security & Privacy Training as well as their Signed Rules of Behavior
   - If you are **new user** and need a mainframe account you must first have your Local CUPS/ACRS POC set up your account.
   - If Access is needed to the Workload and/or DSS mainframe SAS Files the box labeled ZOS **(Mainframe)** should be checked.
   - If Access is needed to the DSS and/or VSSC Web Reports the Box labeled **OTHER** should be checked and **NSSD** entered where it says "specify."
   - If you have an account and need your account modified check the box that says Modify Existing Customer. For example you would need to have your account modified if you have an account for Scrambled SSN access but now you need VISN or National Real SSN Access.

- The individual requesting the access should fill out the information according to the instructions attached to the form. The **Customer ID** is the **Mainframe Account ID** and should be entered if the individual has one.
- Select/determine the Functional Task Code(s) from the list below for the access you require. (Only these codes should be entered on the 9957 since just these codes are coordinated through National Data Systems. Other codes should be coordinated with the appropriate Data Steward on a separate 9957 if required.):
  - 110TT01 (Nationwide Workload Real SSN – Medical SAS Files & VSSC Web Reports)
  - 110TT05 (VISN Level Workload Real SSN – Medical SAS Files & VSSC Web Reports)
  - 110TT13 (Nationwide DSS Real SSN - DSS SAS Files & DSS Web Reports)
  - 110TT12 (VISN Level DSS Real SSN – DSS SAS Files & DSS Web Reports)
  - 110TT20 (Vital Status Real SSN File)
  - 110NN06 (Vital Status Scrambled SSN File) – Requires special Rules of Behavior
  - 110JJ02 (BIRLS Death File)
- Check the add box for each functional code.
- Under Name of Functional Task Code enter the numerical Functional Task Code including all of the information attached to the numeric code in the above list. Select/indicate the type of access you require.
- Under Define Level of Access Requested or Concurring System Manager of Record, enter name of the NDS Director for all the Functional Task Codes EXCEPT 110TT13. For this code you will enter the name of the **Director of DSS Support Office**.

3) The signatures section should be filled out as follows:
   - *Section A. Requesting Official & Title.* This is the individual who will be <u>granted the access</u> and is named in the Customer Information Section. Be sure the name, title, and date are typed before the individual signs the form. All names, titles, and signatures must be readable in versions sent to National Data Systems.
   - *Section C. Approving Official & Title.* This is the name of the <u>individuals immediate Supervisor</u> or the Principal Investigator for the project the individual requires the access. Be sure the name, title, and date are typed before the individual signs the form. All names, titles, and signatures must be readable in versions sent to National Data Systems.
   - *Section E. Second Approving Official & Title.* This is the <u>VAHCS Director</u>, VISN Director, or Program Office Chief. Be sure the name, title, and date are typed before the individual signs the form. All names, titles, and signatures must be readable in versions sent to National Data Systems.

- *G. Name and Title of Facility Point of Contact or Information Security Officer.* At the Durham VAHCSthe two individuals that can be listed as points of contact are the IT Specialist and Account Administrator, Office of Information and Technology or the Supervisor Desktop Support, Office of Information and Technology.

2.2 Routing of Form 9957

1) Do not send VA Form 9957 directly to the Medical Center Director for signature.

2) When the form has been completed through Section C, but prior to getting the Medical Center Director's signature in Section E, the form must be routed to the General Medical Research Secretary. (If the ACOS, Research and Development is the signatory for Section C, route the form to the General Medical Research Secretary for ACOS, Research and Development signature after Section A has been signed).

3) The document should be sent as an attachment via e-mail to the Research Secretary. The body of the e-mail should include a very brief overview [1-2 sentence(s)] of the project's need for database access.

4) Any request should come from either an IRB-approved protocol or a protocol that will undergo IRB review.

5) The Research Secretary will generate a hard-copy of the data access request and forward it to the Protocol Office. The Protocol Office will determine whether the PI request for access is consistent with an IRB-approved protocol or a pending/expected protocol. Also, a copy of the form will be kept on file by the Research Office.

6) The Research Secretary will generate a hard copy of the data access request and will route it for concurrence through the ACOS, Research and Development and the Chief of Staff. After obtaining the Chief of Staff's concurrence the hard-copy form will be returned to Research.

7) The Research Secretary will then generate an e-mail with the original electronic form attached that will be forwarded to the Director. The e-mail will indicate that the request is for data access related to an approved or pending research protocol and that the ACOS, Research and Development and the Chief of Staff concur with the request.

8) When the Director has provided an electronic signature the document will be returned via e-mail attachment to the requestor.

3 Responsibility

3.1 Requestor (Customer)

It is the responsibility of the requestor to properly and completely fill out VA Form 9957. Once completed per the instructions, the requestor must insure that the digital document(s) are forwarded to the General Medical Research Secretary and are not forwarded directly to the Medical Center Director. Once the document has been completed with all necessary digital signatures and returned to the requestor, it is the responsibility of the requestor to forward the completed document to the appropriate VA entity.

3.2 General Medical Research Office

It is the responsibility of the General Medical Research Office to process requests using VA Form 9957. Once obtained by the Research Office, a copy will be forwarded to the protocol office for review and filing. The Research Secretary will then obtain the necessary concurrences prior to submitting the request(s) to the Medical Center Director for signature. The Research Office is responsible for obtaining the Medical Center Director's signature and returning the completed document to the requestor.

SC 507: RESEARCH DATA REPOSITORIES

1 Policy

This policy defines procedures for review and approval of research data repositories located at the Durham VAHCS, including the establishment and use of research repositories and the use at the Durham VAHCS of data from either on- or off-site repositories.

2 Scope

This policy applies to data collected during the course of a research protocol and maintained for use in future research. In addition, this policy applies to research repositories established by Durham VAHCS investigators and to Durham VAHCS investigators who obtain data for research use from other research repositories (both internal at the Durham VAHCS and all outside repositories).

This policy does not apply to research data collected for specific research protocols. For more detailed information on research data repositories, see VHA Handbook 1200.12, Use of Data and Data Repositories in VHA Research.

2.1 Definitions

Coded Data: Data for which a link (or code) exists to identifiable information about the individual from/for whom the data was collected.

Contributing Investigator: An investigator who deposits data into an established research repository using a procedure approved by the repository owner and the IRB and/or R&DC.

Data: Information derived directly from patients or human research subjects or indirectly through accessing databases or electronic medical records. For the purposes of this policy, it does not include information derived from research involving animals or other types of research that do not involve human subjects.

Data Repository: A database or a collection of databases that have been created or organized to facilitate the conduct of multiple research protocols, including future protocols not yet envisioned. It may also have been created for other purposes such as administrative and clinical purposes. The terms “data repository and “data warehouse” have the same meaning.

Data Transfer Agreement/Data Use Agreement (DTA/DUA): A written agreement between the provider and the recipient of data that are transferred from one to the other. It defines what data may be used, how the data will be used, who may access and use the data, how the data must be stored and secured, and how the recipient will dispose of the data after completion of the research.

De-Identified Data: Data that cannot be linked to a specific individual either because the existing link (such as code key) to the identity of the individual was destroyed or because the data was completely de-identified at the time of collection. De-identified data lack all 18 personal identifiers specified by the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Identifiable Data: Data labeled with personal identifiers (e.g., name, medical record number, social security number, laboratory accession number, or any elements of dates except year alone). Any of the identifiers specified under HIPAA constitutes a personal identifier.

Future Research: Research not covered by the protocol under which the data were originally collected.

Human Subject: A living individual about whom an investigator conducting research obtains (a) data through intervention or interaction with the individual or (b) identifiable private information.

> **Intervention** includes both physical procedures by which data are gathered (for example, venipuncture) and manipulation of the subject or the subject's environment that are performed for research purposes.
> **Interaction** includes communication or interpersonal contact between investigator and subject.
> **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). Private information must be **individually identifiable** (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

Recipient Investigator: An investigator who obtains or receives data from a research repository using procedures approved by the repository owner and the IRB and/or R&DC.

Research Repository Administrator: The person responsible for administering a research data repository. An investigator under a WOC or IPA appointment may not serve as the sole administrator of a VA data repository. Without Compensation (WOC) employees who wish to establish a research repository should consult with the ACOS/R&D.

Research Data Repository: A data repository created from data obtained either to conduct a research protocol(s) or gathered in the course of conducting a research

protocol and is maintained after the completion of the research protocol. The protocol may be a primary research project designed to prove or disprove a specific hypothesis or it may be a protocol specifically designed to collect data (either a one-time-only collection of data or an ongoing collection) that will be placed in a research data repository for future use. A research data repository can be created only after a research repository protocol is developed and approved by the IRB (if human research is involved) and the R&D Committee.

2.2. Data

VA investigators may use VA and VHA data, including data from existing treatment, payment, operations, or research data repositories, etc., to prepare a VA research protocol, conduct VA-approved research, or to create or maintain a VA research data repository. VA investigators may obtain only the minimum amount of data that are necessary to conduct the research (i.e., minimum necessary data).

2.2.1 Sources of Data

Data used for research purposes within VA may come from many different sources, and those sources may be internal or external to VA. Sources of data include:

1) **Data Obtained Directly from Research Subjects.** Data may be collected from research subjects directly through such means as medical tests, interventions, questionnaires, or surveys.

2) **Data Obtained from Sources other than Directly from the Subject.** Data may be collected from indirect sources such other research projects or research data repositories if appropriate approval has been obtained for such re-use of the data. Data also may be collected from non-research sources such as from a third party, or from review of the subject's administrative, medical, or other records. Use or reuse for research of data obtained from indirect sources, including other research projects, must obtain the same IRB or R&D Committee approvals as any other research project.

3) **Research Data Repository.** Research data are not considered to constitute a "research data repository" and are not subject to these requirements if the data are:
   a) Collected for a specific research protocol;
   b) Never used for any other research purpose while retained for the research project for which the data were collected; and
   c) Destroyed after the required record retention period.

These data may not be used for other research purposes unless allowed by the informed consent under which they were collected, approved by the IRB, and placed in a research data repository.

2.2.2 Data Collection

Identifiable data may be collected once the PI has obtained an individual's informed consent and HIPAA authorization (using IRB-approved consent forms and HIPAA authorizations), or the IRB finds that all criteria are met to waive the requirement for a research informed consent and a HIPAA authorization.

De-identified data may be collected without informed consent or HIPAA authorization after the protocol has received the appropriate approvals. Reminder: The PI cannot determine data are de-identified; the PI must receive verification from the IRB and the Privacy Officer. A protocol involving only de-identified data only requires approval by the R&D Committee. The R&D Committee must confirm the data are de-identified.

Note: If the investigator must review identifiable data prior to the data being de-identified, then an informed consent and HIPAA authorization must be obtained from the individual or the IRB must waive the informed consent and HIPAA authorization. If exempt from IRB review under the Common Rule (an informed consent or waiver of informed consent is not required), a HIPAA authorization or waiver of authorization by an IRB or Privacy Board (PB) may still be required.

2.2.3 Data Distribution

Once data (identifiable or de-identified) have been transferred from the Durham VAHCS, the Durham VAHCS's IRB and/or R&DC is no longer responsible for reviewing and approving research protocols accessing those data, if no part of the research is to be conducted at Durham or with Durham's resources (e.g., staff, equipment).

The transfer of the data must be in compliance with all VA privacy and information security requirements.

2.3 Establishing and Administering a Research Data Repository

All research data repositories must be physically located within the space owned or leased by the Durham VAHCS.

2.3.1 Administration and Oversight

All research data repositories must have a principal investigator (PI) and a research repository administrator (one individual may assume both roles). The research repository administrator is responsible for:

1) Developing policies and procedures that include requirements for releasing data from the repository and mechanisms for verifying approval of the research by the IRB(s) if the request is for identifiable data, and R&D Committee(s) of record for the investigator(s) who is requesting the data;

2) Reviewing requests to access data;

3) Keeping records;

4) Maintaining the privacy of subjects and the confidentiality of the data in the repository;

5) Ensuring data in the repository are stored and secured according to VA requirements; and

6) Ensuring that the repository has a Scientific Oversight Committee and an Ethics Oversight Committee. One committee that performs both functions may be created.

   a) **Scientific Oversight Committee**
      i) This Committee should be composed of investigators with scientific expertise and experience with data from databases or data repositories, health systems research, epidemiology, statistics, and any disease areas related to the intended uses of the data.

      ii) This committee is responsible for assisting the data repository administrator in developing policy on the use of the data and for providing technical and scientific recommendations to the research repository administrator and investigators wishing to access data in the data repository.

      iii) Depending on the data repository's written procedures, the committee may approve or disapprove data use requests or make recommendation to the administrators of the data repository to approve or disapprove data use requests.

   b) **Ethics Oversight Committee**
      i) This Committee should be composed of experts in the ethical and legal implications of research involving human subjects, use of large data bases or data from data repositories, as well as experts in the relevant scientific disciplines.

      ii) This Committee is responsible for reviewing requests for data for the protection of human research subjects and advising the database owner or administrator on possible actions related to the requests, and providing an impartial review of the repository's activities, including policies, procedures, and proposals for use of stored data.

A concerted effort must be made to ensure that the administrative oversight of the research data repository remains stable. Measures to ensure stable administrative oversight include:

1) Obtaining approval from the IRB (as applicable) and R&DC for any proposed changes in administrative oversight.

2) Ensuring continued control of the data and compliance with current VA and VHA requirements if administrative oversight is transferred to another qualified VA-compensated investigator or administrator.

3) Combining the research data repository with another VA research data repository.

The IRB (if applicable) and the R&DC must approve the appointment of a new administrator of a research data repository and/or combining research data repositories.

2.3.2 Records

Regardless of applicable administrative controls, adequate records of activities and operations of the research data repository must be maintained. The standard operating procedures (SOPs) for the data repository determine who is responsible for maintaining records and how the records must be maintained. Data and record retention requirements apply to data repository records.

Records include, but are not limited to:

1) Records of all sources of data deposited in the research data repository, including type of data; the date the data were deposited; and copies of the protocols, including the approved consent form template and HIPAA authorization template under which original data were collected. *NOTE: If the data are derived from an administrative data repository, provide evidence that informed consent and HIPAA authorization were not required for its protection*.

2) Records regarding any new use of the data. These records must include: a copy of the new use protocol, the protocol's PI, and official IRB and R&D Committee approval notifications, including: initial and continuing review, documentation of waivers of informed consent and HIPAA Privacy Rule authorization (where appropriate), Access Agreements, Combined DUA-DTAs, and all records of disposition of data after termination of the protocol.

3) Record of data distribution, including the location where the data will be stored and the name(s) and location(s) of the individual receiving the data.

4) Records of all communication with investigators requesting and receiving permission to use data.

5) Records of research data disclosure to a subject, a subject's family, a subject's physician, or a third party, where legally permitted.

6) Minutes of meetings of the Scientific Oversight Committee, the Ethics Oversight Committee, when applicable, including attendance, discussion, and votes.

7) Records of all IRB and R&D Committee actions relevant to the research data repository.

2.3.3 Standard Operating Procedures

The research data repository must have and use written SOPs. The SOPs must address, at least, the following subjects:

1) Administrative activities;
2) Conflict of interest (COI);
3) Tracking of data;
4) Reuse of data including who may approve the reuse;
5) Disclosure to subjects and conditions under which disclosure is or is not allowed;
6) Destruction of data due to the repository's termination;
7) Access agreements (i.e., Combined DUA-DTA);
8) Requiring and maintaining protocols and IRB and R&D Committee approvals; and
9) Security and oversight.

2.3.4 Reporting Requirements

All privacy and security incidents regarding the VA research data repository must be reported in accordance with VA Incident Response policies and requirements.

A report on the research data repository's status must be made to the IRB and the R&D Committee at the VA facility housing the research data repository, at an interval determined by the IRB or the R&D Committee, but at least annually. This report must include, but not be limited to, a description of the following:

1) The sources of data being added to the research repository and the protocol(s) under which they were collected.

2) The type of data released to others for use, the protocol(s) under which they were used, and the planned disposition of the data once the protocol is terminated.

3) Any events involving risk to subjects or others, such as a breach of privacy or confidentiality. ***NOTE:*** *Problems may need to be reported promptly depending on the nature of the risk, the incident, and current applicable reporting requirements*.

4) Findings linking a negative impact on the health status of individuals in the data repository with identified causal factors, including whether there may be a clinical intervention.

5) Current reporting requirements for active protocols. The reporting requirements include those for continuing review, unanticipated problems involving risks to subjects or others, departures from the protocol (deviations), and termination of protocols. Risks to institutions may also be appropriate for reporting.

2.3.5 Conflict of interest (COI)

All COI must be identified and managed in compliance with applicable COI regulations and policies including those of VHA, criminal COI statutes at 18 U.S.C. 11,and the Executive Branch Standards of Conduct at 5 CFR Part 2635. The investigator, research repository administrator, and any other key personnel associated with the repository must disclose any COI as provided in VA and VHA policies on COI and they must seek advice on resolving identified conflicts from a VA ethics official at the Office of General Counsel or Regional Counsel.

1) **Financial COI.** The IRB may determine that direct commercial ties must be discussed during the informed consent process. In addition, the IRB may require that a mechanism for appropriately managing such COI must be developed in consultation with a VA ethics official.

2) **Role conflict and conflict of responsibilities.** If the investigator or repository administrator is both the medical caregiver and the investigator, the investigator must be aware of the potential conflicts created by functioning in dual roles (caregiver and researcher) and ensure that they are appropriately managed. This management of the COI may require such actions by the IRB or others that may include reassignment of responsibilities of an investigator to another qualified individual who does not have a COI. Investigators need to be mindful of potential conflicts created by their own unique personal or professional relationships, roles, and responsibilities. In determining if a COI exists and in resolving any such conflict identified, investigators must seek the advice of the ACOS/R&D, VA regional counsel or the VA-designated ethics officer, as appropriate.

2.3.6 Destruction of Data

If the data are collected under an informed consent, the informed consent under which the data were collected must include the possible options for disposition of the data.

Data may need to be destroyed if appropriate control of the data and compliance with VA and VHA requirements cannot be maintained. Destruction of data in a data repository must be done in accordance with all VA and VHA records disposition requirements. Decisions regarding disposal or disposition of the data must be made by the responsible oversight committee(s) (e.g., IRB or R&DC).

After the data or record retention period has ended, the data is either to be destroyed per current VHA Records Control Schedule for research records or, if appropriate approvals have been obtained for such re-use of the data, placed in another research data repository.

2.3.7 Termination

A research data repository may be terminated only under the direction of the IRB or R&D Committee responsible for the oversight of the repository.

2.4 Using Data From a Research Data Repository

All requests to obtain data must be described in a research protocol and approved by the IRB (if applicable) and the R&DC. Such requests must have a Principal Investigator (usually the recipient researcher) who is responsible for the use of the data. The request for access must then be approved by the repository's administrator in accordance with the repository's written procedures.

In considering the proposed research, the IRB and R&DC must review sufficient information from the investigator to adequately assess the request including if the data to be used are reasonable and necessary to conduct the research. Each committee must also review the source of the data and the purpose for which the data were originally collected, including whether they were collected for research purposes.

The Investigator must provide the following information to assist the IRB (if applicable) and R&DC in their review:

1) If the data were collected for other research projects, whether the reuse is consistent with the consent under which they were collected.

2) If the data were collected for administrative or clinical reasons whether the guidelines under which they were collected allow for storage in a specific data repository and reuse for research purposes.

3) If the data is to be obtained from an administrative or clinical data repository, whether the administrative policies and procedures for the data repository allow for use of the data for research purposes, and if so, whether they allow for it as

identified, de-identified, or coded. ***NOTE:*** *Although some data obtained from an administrative or clinical data repository may be used for a research protocol, the administrative policies for the administrative or clinical repository may not allow the data to be placed in a research data repository for reuse, and use in any other research projects would require requesting the data from the original source repository.*

4) If the data were collected during the conduct of a previous research protocol, the reuse in the new protocol is consistent with the original informed consent. If it is not, or the original informed consent did not address the reuse of the data, the R&D Committee must receive documentation that the IRB specifically-approved the proposed reuse. ***NOTE:*** *If the informed consent states specifically the data will not be reused for other purposes, it cannot be reused*. Reuse may be approved where:
   a) The subjects must again provide consent and a new HIPAA authorization must be obtained;
   b) The subject's name, SSN, scrambled SSN, or date of birth are not used, plus all criteria are met to waive informed consent and waive HIPAA authorization;
   c) The research is exempt from IRB review (38 CFR 16.101), and the criteria for waiver of HIPAA authorization have been met; or
   d) The data are de-identified.

5) A description of the data including if they are identified, de-identified, or coded. If the data are identified or coded, a justification for use of this type of data is required.

6) A justification for the use of real SSNs, if they are requested.

7) Information on data storage and security including:

   a) All locations where the data is to be stored, accessed, or used including servers, desktop personal computers, laptops, non-VA locations, or portable media. ***NOTE:*** *The subject's contact information including name, address, SSN, and phone number need to be maintained in a separate file at the VA and be linked with the remainder of the subject's data only when it is necessary to conduct the research.*

   b) Information on the need and mechanism for copying data from a secure VA server and transmitting or transporting data to other locations.

   c) Plans for the destruction of data if they are not to be placed in a data repository after the protocol is completed and the retention period has expired.

8) Information on any plans to contact, re-contact, or recruit the patients or individuals for further information, or to recruit them for any other research project.

9) How the privacy and confidentiality of subjects associated with the data is to be maintained.

10) Information on any plans to use the current data and the data obtained from the proposed project for future research. If data is to be retained for future research, the protocol must describe the repository in which they are to be maintained, its location, and its security measures. ***NOTE:*** *If the data are retained for future research, the data repository must be established and maintained in accordance with VHA Handbook 1200.12.*

11) Plans for data to be released outside VA. A discussion regarding why this release is consistent with the VHA policy, the Privacy Act, and HIPAA must occur.

12) Information on the PI's ability to finish the protocol.

13) Documentation that all research team members are to be working within their scope of practice, privileges, or functional statements.

2.5 Preparatory to Research

Data repositories may be used by VA investigators for activities that are preparatory to VA research without the requirement to obtain either a HIPAA authorization from the subject or waiver of HIPAA authorization by an IRB or a Privacy Board (PB). This includes use of PHI for the preparation of a research protocol prior to submission to the IRB(s) or R&D Committee(s). "Preparatory to Research" activity is the only instance of access for research purposes allowed in VHA without a written HIPAA authorization signed by the individual, a waiver of HIPAA authorization by an IRB or PB, or approval by the R&D Committee(s) and the IRB(s). This access is granted only to VHA researchers. Non-VHA researchers may not access VHA data for reviews preparatory to research. For additional information, see HRPP SOP IC 704, Privacy Rule and Research.

3 Responsibility

3.1 Institutional Review Board (IRB)

If the research data repository is created at and housed at the Durham VAHCS, the IRB is responsible for reviewing and approving the creation and operations of the research data repository and for conducting reviews of the research repository's activities at least once a year.

The Durham VAHCS IRB is responsible for approving individual research protocols that propose to use data from a research data repository if the investigator is from the

Durham VAHCS and it is a Durham VAHCS research data repository, or if the research data repository standard operating procedures require such approval.

In addition to receiving sufficient information from the investigator to adequately assess the request, if a Durham VAHCS Investigator wishes to use data from a data repository (research or non-research), the Durham VAHCS IRB must:

1) Determine whether or not the project is research as defined by the Common Rule as found in 38 CFR 16.102(d).

2) Determine, if the research activity is human subjects research, if it is exempt from review by the IRB in accordance with 38 CFR 16.101(b).

3) Approve or exempt the protocol from IRB review.

4) Waive informed consent and HIPAA authorization if the appropriate criteria are met. If the research does not meet the criteria, the IRB must approve a written informed consent form and the investigator must obtain informed consent from each subject. If the requirements for waiver of the HIPAA authorization have not been met, the investigator must obtain a written authorization from each subject.

5) Ensure that if the data were collected during the conduct of a previous research protocol, the reuse in the new protocol is consistent with the original informed consent. If it is not, or the original informed consent did not address the reuse of the data, the IRB must specifically approve the proposed reuse. ***NOTE:*** *If the informed consent states specifically that the data will not be used for other purposes, it cannot be reused.* Reuse may be approved where:
   a) The subjects must again provide consent and a new HIPAA authorization must be obtained;
   b) The subject's name, SSN, scrambled SSN, or date of birth are not used, plus all criteria are met to waive informed consent and waive HIPAA authorization;
   c) HIPAA authorization requirements have been met; or
   d) The data are de-identified prior to use.

6) Perform continuing review, unless the protocol is determined to be exempt.

7) Ensure the data accessed from the data repository are required by the approved protocol and used only for the purposes defined in the approved protocol. Reuse of the data may not occur without approval of a new protocol, unless the use is preparatory to research.

8) Approve the research. To approve the research, the IRB must make all determinations required by 38 CFR 16.111. In addition, the IRB must determine if

the use of the data is allowed by and is consistent with both the Privacy Act of 1974 and the HIPAA Privacy Rule.

9) When acting as a Privacy Board, ensure that all HIPAA Privacy Rule requirements have been fulfilled.

10) Obtain the assistance of ad hoc reviewers or consultants including the facility's Privacy Officer and ISO, as needed.

3.2 Research and Development Committee (R&DC)

The R&DC is responsible for reviewing and approving the creation and operation of the research data repository, including the research repository SOPs. The R&DC will conduct reviews of the research repository's activities at least once a year.

The Durham R&DC is responsible for approving individual research protocols that propose to use data from a research data repository if the investigator is from the Durham VAHCS and it is a Durham VAHCS research data repository, or if the research data repository standard operating procedures require such approval.

In addition to receiving sufficient information from the investigator to adequately assess the request, if a Durham VAHCS Investigator wishes to use data from a data repository (research or non-research), the Durham VAHCS R&DC must:

1) Ensure that if the data were collected during the conduct of a previous research protocol, the reuse in the new protocol is consistent with the original informed consent. If it is not, or the original informed consent did not address the reuse of the data, the R&D Committee must receive documentation that the IRB specifically-approved the proposed reuse. ***NOTE:*** *If the informed consent states specifically the data will not be reused for other purposes, it cannot be reused*. Reuse may be approved where:
   a) The subjects must again provide consent and a new HIPAA authorization must be obtained;
   b) The subject's name, SSN, scrambled SSN, or date of birth are not used, plus all criteria are met to waive informed consent and waive HIPAA authorization;
   c) HIPAA authorization requirements have been met; or
   d) The data are de-identified prior to use.

2) Perform a continuing review of the protocol.

3) Ensure the data accessed from the data repository are required by the approved protocol and used only for the purposes defined in the approved protocol. Reuse of

the data may not occur without approval of a new protocol unless the use is preparatory to research.

3.3 Associate Chief of Staff for Research & Development (ACOS/R&D)

The ACOS/R&D is responsible for assisting the research repository administrator in developing standard operating procedures on the use of the data and for providing technical and scientific recommendations as needed.

3.4 Research Repository Administrator

The Research Repository Administrator is responsible for creating detailed research repository standard operating procedures (SOPs) and providing those SOPs to the IRB (if applicable) and R&DC for review and approval before establishing a research repository at the Durham VAHCS. Once a research repository is approved by the IRB and or R&DC the research repository administrator is responsible for the acquisition and maintenance of all data, reviewing requests to access/release data, keeping records, maintaining the privacy of subjects and the confidentiality of the data, ensuring data in the research repository are stored and secured according to VA requirements, and initiating data use agreements (DUAs) or data transfer agreements (DTAs) as needed with recipient investigators.

3.5 Investigator

The investigator's primary responsibilities for designing and conducting research involving the use of data repositories are similar to those for other types of studies. If the protocol involves human subjects then all policies related to human subjects research are applicable. In addition, the protocol must incorporate all information required by the review committees per this guidance.

No research involving data repositories can be initiated before the investigator(s) obtains all required approvals in writing.

The investigator is responsible for maintaining the privacy and confidentiality of all PHI and sensitive data in accordance with applicable VA and VHA information confidentiality and security requirements.

CO 601: REPORTING TO OTHER ENTITIES

1. Policy

The IRB is required by federal regulation and institutional policy to communicate certain actions to entities that may have an interest in the status of the research being conducted. VA facilities and investigators are required to comply with all applicable reporting requirements of relevant Federal and state oversight agencies, funding entities, and the sponsor(s).

Reportable research events will be promptly reported to the VA facility Director, relevant Federal agencies, including ORO and/or ORD (when applicable), OHRP, NIH (when applicable) and FDA (for FDA-regulated research) of for cause suspensions of IRB approved research projects and of any serious unanticipated problems involving risks to subjects or others and the resolution of those problems.

1.1 Communications to Others

The purpose of this policy is to ensure prompt reporting to appropriate Institutional Officials, funding sources, agency heads, regulatory agencies and any other appropriate entity of any of the following IRB actions:

- Determination that an event represents an unanticipated problem involving risks or harm to human subjects or others.
- Determination that noncompliance was serious or continuing.
- Any suspension or termination of IRB approval.

1.1.1 Reports to ORO Subject Matter Expert (SME) Groups:

The Facility Director must report the following research events to the appropriate ORO SME group as soon as possible but no later than 5 business days after being informed:

1) Problems in VA Research: Any problem in VA research that is determined by IRB review to involve serious risks to subjects or others, and be unanticipated and related, or probably related to the research.
2) Adverse Events (AE): Any AE in VA research that is determined by IRB review to be serious (SAE) and unanticipated and related, or probably related, to the research.
3) Serious or Continuing Noncompliance: Noncompliance determined by the IRB to be serious or continuing.
    a. Reports based on findings made by entities external to the facility must include a copy of the entity's official findings.
4) Terminations or Suspensions of IRB Approval: Terminations or suspensions of IRB approval of research that are related to concerns about the safety, rights, or welfare of human research subjects, research staff, or others.

Note: The facility Director's written report is required regardless of whether disposition of the event has been resolved at the time of the report. Follow-up reports detailing any additional findings and appropriate remedial actions must be provided to the relevant ORO office at intervals and in a manner specified by that office.

Initial reports to ORO must include:

1) The name and any relevant Assurance number of the reporting VA facility.
2) The title of the research project(s)
3) The number(s) used by the facility's Research Service or relevant research review committee(s) to identify the project(s).
4) The name of any external sponsor(s) of the project(s).
5) The funding source(s) for the project(s).
6) The name of any agencies or organizations external to VA that were notified, or need to be notified, of the event.
7) A description of the event being reported, including (where applicable) the nature of the research study (e.g., retrospective chart review, cancer treatment study, post-traumatic stress disorder behavioral intervention study, etc.
8) A description of any immediate actions taken to address or investigate the reported event.

Follow-up or interim reports must be provided as directed to incorporate the full scope of relevant determinations and remedial actions, including programmatic actions as warranted.

1.1.2 Reports to ORO

The Facility Director must report the following research events to the appropriate ORO office as soon as possible but no later than 5 business days after being informed of them:

1) Assurance Changes: Any change in the facilities FWA or other ORO-approved Assurance.
2) IRB Changes: Any change in the facility's designated IRB(s).
3) Substantive MOU Changes: Any substantive change in a MOU with an affiliate institution or other entity related to the designation of IRBs or other human research protection arrangements.
4) Accreditation Problems: Failure of the VA facility to achieve the accreditation stats required by ORD for human research protections, any change in the facility's accreditation status, or any change in the accreditation status of an affiliate involved in the facility's human research protection program.
5) Allegation of research misconduct.

6) RCO Changes: An appointment, resignation, or change in status of the facility RCO.

1.1.3 Reports to OHRP

Reports of unanticipated problems, serious or continuing noncompliance, or suspensions or terminations must include:

1) Name of the institution conducting the research.
2) Title of the research project and/or grant proposal in which the problem occurred.
3) Name of the PI on the protocol.
4) Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement).
5) The nature of the event (unanticipated problem involving risks to subjects or others, serious and/or continuing noncompliance, suspension or termination of approval of research).
6) A detailed description of the problem including the findings of the organization and the reasons for the IRB's decision.
7) Actions the institution is taking, or plans to take, to address the problem (e.g., revise the protocol, review the informed consent document, inform enrolled subjects, increase monitoring of subjects, suspend subject enrollment, terminate the research, etc.).
8) Plans, if any, to send a follow-up or final report by whichever occurs sooner:
   - A specific date, or
   - When an investigation has been completed or a corrective action plan has been implemented.

1.2 Other Reportable Events

A. Medical Device Classification

If the IRB determines that a study submitted as a non-significant risk presents significant risk, the IRB must notify the Sponsor and the Investigator in writing.

Investigator Security and Privacy Violations (See RR403, 1.12 Research Information Protection Incidents)

i. Investigators will immediately (within one hour) report (call or email: VHADURResearchEventReport@va.gov) any theft, loss or compromise of any VA sensitive information. The event reporting group, VHADURResearchEventReport@va.gov, contains includes the ISO and

PO. Report lost or stolen computer equipment to the ISO and VA Police (if local). The VA police do not need to be contacted if the lost or stolen devices contain no VA Sensitive Information (VASI) or PHI. If not at the VA, call security at your location (hotel, airport, etc.) and call the local police. Obtain phone #, badge #, case #, and copy of report. In addition, the ACOS/R&D, the ISO, the Privacy Officer and IRB must be notified.

ii. Any theft, loss or compromise of VA sensitive information must be reported to the IRB within 5 business days of becoming aware of any information security or privacy incident using the Report Form for Privacy and/or Information Security Incidents in VA Research. If further reporting is determined to be necessary the ISO will notify the Medical Center Director who will notify VA Central Office. If the incident is believed to involve criminal activity, the ISO and/or PO will contact the local VA Police and the OIG. Research staff will immediately notify the Investigator of any theft, loss, or compromise of VA sensitive information as soon as it is discovered. The Investigator will then follow the above escalation. Lost or stolen devices related to research that contain no VASI or PHI do not need to be reported to the IRB immediately (within 5 days of learning of the event), but will be reported at continuing review on the adverse event log.The IRB Chair (or designee) will notify the medical center Privacy Officer in writing within 5 working days of the convened meeting in which a privacy violation relative to a research protocol is discovered.

2. Scope

These policies and procedures apply to all research submitted to the IRB.

3. Responsibility

IRB Program Administrator is responsible for corresponding with other interested entities concerning the status of research under review by the IRB.

IRB Chairperson (or designee) is responsible for ensuring appropriate discussion and IRB decision-making regarding unapprovable emergency research, risk assessment of investigational device, adverse event assessments, and Investigator non-compliance, where communication with outside entities is necessary.

CO 602: RESEARCH PERSONNEL DRUG SAFETY ALERTS & NOTIFICATION

1. Policy

ADEs must be reported to the national VA Adverse Drug Event Reporting System (VA ADERS), and the Food and Drug Administration (FDA) MedWatch system at http://www.fda.gov/medwatch/safety/FDA-3500A_Fillable.pdf, or adverse events from vaccines to the Centers for Disease Control and Prevention (CDC) and the FDA Vaccine Adverse Event Reporting System (VAERS) at https://vaers.hhs.gov/esub/index.

Durham VAHCS will ensure rapid notification of Investigators, ACOS for R&D, AO for R&D, the IRB and Research and Development Committees of relevant National PBM Bulletins and National PBM Communication Drug Safety Alerts.

Durham VAHCS will also ensure when required, the notification of research subjects involved and any applicable modifications to the research protocol and informed consent to ensure the highest level of protections for the research subjects.

2. Scope

This policy applies to all Durham VAHCS approved interventional human research studies; any study that gather data through interactions with subjects.

3. Responsibilities

A. **Medical Center Director**: Per VHA Directive 1070 the Medical Center Director is responsible for ensuring the medical facility has a local ADE reporting policy which includes written procedures that describe the operation of the facility ADE reporting system through VA ADERS.

1.) Ensuring that the Durham VAHCS Investigator or authorized study personnel documents in CPRS any observed ADEs that occurred or were recognized in association with any FDA-approved drug or biologic used in a research study.

2.) Ensuring that all Durham VAHCS Investigators or authorized study personnel involved in direct patient care receive employee health care orientation training on entering ADEs into CPRS and VA ADERS of any FDA approved drug or biologic.

3.) Ensuring participation of research staff with appropriate departments or groups involved in the ADE process for the coordination of ADE reporting and risk assessments.

C. **Chief of Pharmacy Service:** In addition to those responsibilities found in VHA Handbook 1108.04, the Chief of Pharmacy Service is responsible for:

1.) Maintaining current records of all pharmaceutical products that are being used as either investigational drugs or comparator drugs.

2.) Designating a research pharmacist to serve as liaison to the facilities research program in areas such as: the use of study related drugs, evaluation of the impact of the research on the Pharmacy Service, and review of the research protocol.

3.) Serving as a subject matter expert or designating one, as appropriate for the IRB when necessary.

D. **ACOS for R&D and AO for R&D:** The ACOS for R&D and AO is responsible for:

1.) Creating and maintaining a current electronic database to include all investigational drugs, comparator drugs, or study-related drugs being used in Durham VAHCS human subject research projects, in addition to the name of the Investigator and the study title. Once established, designated Pharmacy Personnel will have shared access to the database.

2.) Reviewing all National PBM Bulletins or National PBM Communications as soon as they are received.

3.) Determining whether or not the specific pharmaceuticals addressed in National PBM Bulletins or National PBM Communications are on the current list of pharmaceutics (investigational drug, comparator drug, and study-related drug) being used in any of the Durham VAHCS's human research protocols. If the pharmaceutical is being used in a protocol, the ACOS for R&D and AO for R&D are responsible for:

a.) Contacting the Investigator (verbally and in writing) as soon as possible and always within 5 working days and forwarding a copy of the National PBM Bulletin or National PBM Communication to the IRB with the name of the study involved.

b.) Ensuring that records are maintained of all notifications and the resulting actions and communications.

c.) Determining in conjunction with the Investigator, the designated Research Pharmacist or other qualified individual, if the report contains information that may indicate an increased risk or potential risk to research subjects, or require changes to any part of the research protocol and informed consent.

4.) Notifying the COS that all research subjects have been notified if notification was required, and that the notification of the research subjects was appropriately documented. If all research subjects were not notified, the COS must be informed in writing that they have not and why they were not notified.

E**. Principal Investigator:** The Principal Investigator is responsible for:

1.) Determining in consultation with the ACOS for R&D, the Chief, Pharmacy Service or other qualified individuals, whether the information in the National PBM Bulletin or National PBM Communication represents apparent immediate harm or potential increased risk to research subjects. If it is determined that there is increased risk or possible harm to research subjects:

a.) A list of research subjects who may be at risk must be compiled.

b.) **Apparent Immediate Harm to the Subjects**. If it is determined that there may be an apparent immediate harm to subjects, the IRB Chair must be notified as soon as possible and no later than 3 working days of the Principal Investigator becoming aware of the apparent immediate harm. The protocol and informed consent must be appropriately amended immediately.

Modifications in the amendment may be instituted prior to IRB approval to eliminate apparent immediate harm to the research subjects. If they are instituted, the IRB Chair must be notified of the actions taken and the amended protocol and consent must be submitted to the IRB as required by VHA policy. ***NOTE**: PBM notification letter will be sent to the Investigators, IRB, and Data Monitoring Committee (DMC).* If applicable and within Durham VAHCS jurisdiction a *DMC will convene within 5 day if practicable, and will submit a summary of their findings to the IRB within 24 hours of the meeting.*

c.) **Possible Increased Risk to Research Subjects**. The IRB Chair must be notified of the possible increased risk to the subject within 5

working days of the Principal Investigator becoming aware of the risk. The notification should be in the form of a memorandum or other document that discusses the new information, the risk to the subjects, and a proposed action plan. The proposed plan may include amendments to the protocol and the informed consent. ***NOTE**: If the PBM alert includes a notification letter for all patients and subjects, the letter must be submitted to the IRB for approval prior to sending it to the subjects unless there is apparent immediate harm to the research subject.*

2.) Initiating all modifications approved or required by the IRB in a timeframe required by the IRB. The implementation of these modifications must be documented in the research record and as appropriate, in the subject's medical record.

3.) **Responding to FDA Withdrawal of Marketed Drugs**: If a research investigational drug, comparator drug, or other drug named in the research informed consent is withdrawn from the market by FDA no new study subjects may be entered into the study. Those subjects already entered into the study will be notified to stop taking the drug, noting how the drug should be stopped, and if any additional follow-up is required.

4) Reporting ADEs on VA approved research studies: All ADEs in research subjects on a clinical trial where the protocol requires the use of investigational drugs, comparator drugs or concurrent drugs or any combination thereof must be reported to VA ADERS if the drug has been approved by the FDA, is being used for an FDA approved indication, and are being used at a dosage and in a patient population that is consistent with the official labeling of the drug .

Reporting in VA ADERS **is not** required if the investigational drugs, comparator drugs or concurrent drugs, or any combination thereof, are:

(1) Under an Investigational New Drug or

(2) Used in a clinical trial in which the investigator does not know participants' treatment assignment because of the use of a blinded methodology.
All other requirements of VHA Directive 1070 should be followed.

IC 701: GENERAL REQUIREMENTS AND DOCUMENTATION OF INFORMED CONSENT

1. Policy

The IRB is responsible for the review and approval of the informed consent form prepared by the Investigator. The consent form must contain all of the required elements and meet all other requirements outlined in SOP IC 701. If the wording of the informed consent has been initially prepared by an entity (e.g., a pharmaceutical company or a cooperative study group including National Cancer Institute (NCI) groups) other than the VA Investigator, the IRB must ensure that the wording of the consent meets all the regulatory requirements. IRB approval of the wording of the consent must be documented through the use of a stamp on each page of the consent form that indicates the date of the most recent IRB approval of the document. If the consent form is amended during the protocol approval period, the form must bear the approval date of the amendment.

A written consent document embodies the elements of informed consent described in 21 CFR 50.25, 38 CFR 16.116 (a), and 45 CFR 46.116(a). This form may be read to the subject or the subject's legally authorized representative, but, in any event, the Investigator shall give either the subject or the representative adequate opportunity to consider whether or not to participate in the research prior to signing the informed consent document. The subject must also be given a copy of the signed form.

Informed consent must be legally effective and prospectively obtained.

Except as described in SOP IC 702, no Investigator may involve a human being as a subject in research unless the Investigator has obtained the legally effective informed consent of the subject or the subject's LAR (38 CFR 16.116). An individual who is qualified to be a LAR for research purposes may not always qualify as a personal representative for purposes of consenting to use or disclose a living subject's PHI (i.e., signing a HIPAA authorization). Therefore, in circumstances involving authorization for use or disclosure of a subject's PHI, the Investigator must ensure the LAR meets the requirements of a personal representative in HIPAA and the Privacy Act of 1974 (legal guardian or power of attorney) prior to the LAR's signing a HIPAA authorization (see VHA Directive 1605.01).

The Durham VAHCS does not use the "short form" when obtaining consent.

1.1 General Requirements for Informed Consent

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

(1) The information that is given to the subject or the representative must be in language understandable to the subject or the representative.

(2) No informed consent process, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive, or appear to waive, any of the subject's legal rights, or releases or appears to release, the investigator, the sponsor, the institution or its agents from liability for negligence.

1.2 Required Elements of Informed Consent

a. Elements of Informed Consent Required by the Common Rule**:** Except as provided with waivers of consent, 38 CFR 16.116(a) requires the following elements of informed consent be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others that may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) An explanation as to whether any compensation is available, and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate involves no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

b. Additional Elements of Informed Consent Required by VA.

The following additional elements of informed consent are required for VA research:

(1) Any payments the subject is to receive for participating in the study;

(2) Any real or apparent conflict of interest by investigators where the research will be performed; and

(3) A statement that VA will provide treatment for research related injury in accordance with applicable federal regulations (see paragraph 25).

c. Additional Elements of Informed Consent.

When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or becomes pregnant) that are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly and safe termination of participation by the subject;

(5) A statement that any significant new findings developed during the course of the research that may relate to the subject’s willingness to continue participation will be provided to the subject;

(6) The approximate number of subjects to be entered in the study; and

(7) When appropriate, a statement that informs VA research subjects that they or their insurance will not be charged for any costs related to the research. NOTE: Some Veterans are required to pay copayments for medical care and services specifically related to their medical care provided by VA. These co-payment requirements will continue to apply to medical care and services that are not part of the research procedures or interventions.

1.3.3 Other Requirements

A. Second person: The language of the consent document should be in the second person style so the consent form conveys a dialogue with information being provided and that there is a choice to be made by the subject rather than presumption of the subject's consent with the use of the first person style.

B. Language should be simple: The information provided in the informed consent documents must be in language understandable to the subject or the subject's legally authorized representative. The informed consent document should not include complex language that would not be understandable to all subjects. Technical and scientific terms should be adequately explained using common or lay terminology. The consent form must be completed using at a minimum 6th grade reading level.

C. Exculpatory language: Informed consent documents (written or oral) may not contain any exculpatory language through which the subject is made to waive or appear to waive legal rights, or releases or appears to release the Investigator, the Sponsor, or the Durham VAHCS from liability for negligence.

D. FDA-regulated test articles: For all research involving test articles regulated by the FDA, informed consent documents must include a statement that the purpose of the study includes evaluation of both the safety and the effectiveness of the test article. The consent form must also include a statement that the FDA has access to the subject's medical records.

E. According to 38 CFR 17.85 "Treatment of Research-Related Injuries to Human Subjects " VA must provide necessary medical treatment (i.e., not just emergency treatment) to a research subject (veteran and non-veteran) injured as a result of participation in a research project approved by a VA R&D Committee and conducted under the supervision of one or more VA employees. Except in limited circumstances, the necessary care must be provided in VA medical facilities. Exceptions include: situations where VA facilities are not capable of furnishing economical care; situations where VA facilities are not capable of furnishing the care or services required; and situations involving a non-veteran research subject. Under these circumstances, Medical Center Directors may contract for such care. Medical Center Directors shall provide reasonable reimbursement for the emergency treatment of a research subject (veteran and non-veteran) in a non-VA facility. This requirement does not apply to treatment for injuries that result from non-compliance by a research subject with study procedures. Unless the requirement is waived, the informed consent form must include language explaining VA's authority to provide medical treatment to research subjects injured by participation in a VA research project. Investigators

must use the following wording in the consent form regardless of funding source to note this requirement: "*The VA will provide necessary medical treatment should you be injured by being in this study. You will be treated for the injury at no cost to you."*

F. The regulation at 38 CFR 17.85 does not apply to research conducted for VA under a contract with an individual or a non-VA institution (although veterans injured as a result of participation in such research may nevertheless be eligible for care from VA under other statutory and regulatory provisions). Information on the responsibility for research-related injury under such circumstances must be included in the consent form.

G. In accordance with 38 United States Code 1710(f) and 1710(g) certain veterans are required to pay co-payments for medical care and services provided by VA. Veterans receiving medical care and services from VA that are not rendered as part of the VA-approved research study must pay any applicable co-payment for such care and services.

   Unless the requirement is waived, Investigators at the Durham VAHCS must use the following wording in the consent form to note this requirement. *"Some veterans are required to pay co-payments for medical care and services provided by VA. These co-payments requirements will continue to apply to medical care and services provided by VA that are not part of this study."*

H. Compensation to Investigators: The Durham VAHCS IRB must approve all recruitment incentives to Investigators, physicians, and other health care providers for identifying and enrolling subjects. Investigators must disclose to the IRB recruitment incentives at initial review and any change in incentives on-going. The IRB reviews the recruitment incentives to assure the incentive does not create undue influence for the Investigator to recruit subjects. The consent form must include the Sponsor's name and a statement that the Investigator will not personally benefit from the study but the sponsor will support the salary of the research team. Payments from an Investigator or sponsor to a person for referral of potential subject s (i.e., finders fees) are permissible when the payment is not to a person in an authority relationship with the prospective participant (e.g., employer-employee, physician-patient, Investigator-subject) and the IRB determines that such payments will not increase the risk of coercion or undue influence upon Investigators or subjects.

   The American Medical Association considers offering or accepting payment to or from a physician for referring patients to research studies (finder's fees) to be unethical.

Payments from a sponsor to an Investigator based on the rate or timing of recruitment are permissible provided that:

- No direct payments are made to the Investigator or staff, and
- Monies are deposited into the Investigator's Institute of Medicine Account for him/her to use for research purposes.

I. Advertisements

All advertisements must be IRB approved prior to posting and distribution. For more information on advertisements, see SOP RR 402 and SOP RI 801.

J. CPRS – Flagging the Medical Record: The IRB will inform Investigators when the patient health record must be flagged to protect the subject's safety by indicating the subject's participation in the study.

Please see SOP RI 803 for specific Investigator responsibilities for flagging the medical record.

K. Tissue/Data Banking Informed Consent Requirements: The consent form should clearly address the following points:

- (1) A description of the biospecimens to be banked/stored and the process for banking/storing them.
- (2) A description of the research to be conducted with the biospecimens including what future research may be performed, if known at the time of collection. It should be stated if DNA and/or RNA will be collected and stored for future studies, when applicable. Note: If the future research is not known at the time of the research study under which the biospecimens are collected or the biorepository's inception, a generalized or broad description of the future research is acceptable; however, if genetic testing is anticipated, it should be mentioned.
- (3) A description of the conditions under which biospecimens will be released to other researchers and whether they will be released outside the VA. These conditions might include the requirement of a Material Transfer Agreement, an IRB approved protocol for use of the biospecimens, etc.
- (4) A description of the risks from biospecimen banking/storage including any risks to privacy and confidentiality, for example, specimen identifiers on the specimen labels, or any data that may be linked to the biospecimens.
- (5) Information about possible consequences of DNA/RNA analyses (such as disclosure of paternity, potential identifiability, implications for family members, etc.) if genetic or genomic research is anticipated. Potential risks may include breach of confidentiality, which may lead to discrimination in the areas of

employment, insurability, social stigmatization, or psychological stress caused by disclosure of adverse information to the subject or the subject's family.

- (6) When and under what conditions research results will be conveyed to the participant, the participant's family, or the participant's physician. NOTE: Individual research results are not normally returned to participants unless directly related to their care, they have been clinically validated, or run in a laboratory that is certified under the Clinical Laboratory Improvement Amendments or CLIA. This does not apply to the mandated reporting of results on Clinical Trials.gov.
- (7) Whether biospecimens may be provided to a for-profit company for the development of products and, if so, whether commercial benefits may be expected for the company and a statement that the participant should not expect to receive any of those benefits.
- (8) What will happen to the biospecimens if the individual withdraws from participation in the biorepository, or research study, before its completion. The informed consent form should clearly state how participants may withdraw their consent and what will happen to their biospecimens if they do withdraw consent. Conditions under which it is not possible to withdraw biospecimens should be clearly explained. For example: Biospecimens may not be able to be withdrawn if they have already been sent out for testing or to outside investigators.
- (9) When biospecimens are collected for future use, or the creation of a biorepository, as an optional component of participation in a research study, the informed consent for banking biospecimens should be a separate section of the main research study informed consent form. Alternatively, there could be a separate informed consent form for the optional biobanking component.
    - (10) If the biorepository or biospecimen collection will be stored outside of the United States at the time of study initiation, the country of storage should be stated in the informed consent.

Please see SOP 801 for specific Investigator Responsibilities for Banking Specimens.

L. Data Retention When Subjects Withdraw from a Clinical Trial

For FDA-regulated research:

- When a subject withdraws from a study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed. The consent document cannot give the subject the option of having data removed.
- An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject distinguishes

between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive c hart review, and address the maintenance of privacy and confidentiality of the subject's information.

- The investigator must obtain the subject's consent for this limited participation in the study (assuming such a situation was not described in the original consent document). The IRB must approve the consent document.
- If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

1.3.4 ClinicalTrials.gov Requirements

For applicable clinical trials initiated on or after March 7, 2012, informed consent documents must be in compliance with the new requirement in 21 CFR § 50.25(c) and include a specific statement that refers to the trial's description on www.ClinicalTrials.gov.

The investigator and sponsor are responsible for determining whether a trial is an applicable clinical trial and to include the required statement in the informed consent document, as appropriate, for approval by the IRB.

"Applicable clinical trials" generally include controlled interventional studies of drugs, biological products, or devices that are subject to FDA regulation, meaning that the trial has one or more sites in the United States, involves a drug, biologic, or device that is manufactured in the United States (or its territories), or is conducted under an investigational new drug application (IND) or investigational device exemption (IDE):

> The trial is an "applicable clinical **device** trial" if the trial prospectively compares a device-based intervention subject to FDA regulation against a control in human subjects; or the trial is a pediatric post-market surveillance trial.
>
> The trial is an "applicable clinical **drug** trial" if the trial is a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to FDA regulation. For the purposes of this definition, a "clinical investigation" is "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects."

The following statement must be reproduced word-for-word in informed consent documents for applicable clinical trials:

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

Do not include the statement in the ICF if the study is not required to be listed on Clinicaltrials.gov and the PI has no intention of listing it there.

Even if a waiver of documented informed consent is approved, the trial participant still provides consent and the statement is required during the oral presentation of the research and/or in the written statement regarding the research, if required by the IRB.

Do not include the statement in the ICF if the study is not required to be listed on Clinicaltrials.gov and the PI has no intention of listing it there.

1.4 Consent for Photographs, Voice, or Video Recordings for Research Purposes

The research informed consent process must include information describing any photographs, video, and/or audio recordings to be taken or obtained for research purposes, how those items will be used for research, and whether those items will be disclosed outside VA.

An informed consent process to take a photograph, video, and/or audio recording cannot be waived by the IRB. Note that in certain instances (e.g., phone or internet survey when data does not leave VA) the IRB may grant a waiver of documentation of informed consent (the participant does not sign a consent form) and a HIPAA waiver.

The consent for research does not give legal authority to disclose the photographs, videos, and/or audio recordings outside VA. A HIPAA authorization is needed to make such disclosures. If the photograph, video, and/or audio recording will be shared with non-VHA entities, then the Investigator must obtain a signed HIPAA authorization.

If the photograph, video, and/or audio recording will not be shared outside of VA and if the materials are not collected on VA property, then it is sufficient for the PI to conduct an informed consent process that includes information about the recording in the consent (i.e., in-person with an informed consent form), or consent script (i.e., an informed consent process with an ICF waiver of documentation), to have a HIPAA

waiver in place, to document verbal consent (if applicable), and record in each separate session the Veteran's verbal consent to be recorded.

VA Form 10-5345, Request for and Authorization to Release Medical Records or Health Information, documents permission for the disclosure of medical records or health information, including pictures, video, and voice recordings to another individual. In the conduct of research, VA Form 10-5345 must be used in accordance with applicable VA and VHA policy.

1.5 Documentation of Informed Consent

Informed consent must be documented prospectively by the use of a written consent form approved by the IRB (38 CFR 16.117(a), unless documentation of informed consent has been explicitly waived by the IRB (38 CFR 16.117(c)). ***NOTE:*** *Email communications do not constitute documentation of informed consent.* The form may be read to the subject of the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

a. Consent Form. Investigators should use the current Durham VAHCS IRB-approved informed consent form template as a basis for consent documents. The DoD informed consent form may be employed for active duty military personnel participating in VA research at DoD sites when VA-specific language is not necessary (e.g., when language for treatment of research related-injury is not needed because active duty military personnel are covered by DoD). For DoD research, the IRB must determine that the disclosure includes provisions for research-related injury that follow the requirements of the DoD Component. The informed consent form must be the most recent IRB-approved informed consent form that includes all the required elements and, as appropriate, additional elements.

(1) The requirement to utilize the current Durham VAHCS IRB-approved informed consent form template to document informed consent applies to all VA-approved research including, but not limited to, studies in which VA Investigators working on VA Research enroll subjects at the affiliate hospital or other sites outside VA (e.g., community centers or shopping malls).

(2) The "most recent" IRB-approved version of the informed consent form contains the date of the version of the informed consent form most recently approved by the IRB (e.g., in a header or footer). For instance, if the most recent version of the informed consent sent for approval by the IRB was the June 14, 2009, version, and

the IRB approved it on July 1, 2009, the Investigator must ensure the informed consent form contains the date June 14, 2009, on each page. The June 14, 2009, version would continue to be the most recent version even after approval by the IRB during the continuing review process (i.e., if there is no change in the informed consent form at the time of continuing review, it is not considered a new version).

b. IRB Approval Date. The IRB approval must be documented in the IRB minutes or IRB protocol files for those studies reviewed by the expedited process. IRB correspondence with the Investigator must clearly indicate which version of the informed consent form has been approved. The IRB approval date must be documented by the use of a stamp or preprinted box on the first page of the informed consent form. This stamp or preprinted box must indicate the most recent date of IRB approval of the informed consent form. The IRB must maintain a copy of the approved informed consent form in its records.

c. Signatures and Dates**.** The informed consent form must be signed and dated by:

(1) The subject or the subject's LAR (38 CFR 16.117(a)),

(2) The person obtaining the informed consent, and

(3) A witness, if required by IRB (e.g., the IRB may require a witness if the study involves an invasive intervention or an investigational drug or device).

(a) The witness is required to witness only the subject's or subject's LAR's signature, not the informed consent process (e.g., if the subject does not want the witness to know the nature of the research study), unless the sponsor or IRB requires the witness to witness the informed consent process.

(b) The witness cannot be the person who obtained informed consent from the subject, but may be another member of the study team or may be a family member.

d. Original Signed Consent Form. The original signed and dated informed consent form must be filed in the Investigator's research file for that subject so that it is readily accessible for auditing and secure. If the subject submits the signed and dated informed consent form to the Investigator or designee by facsimile, the person who obtains informed consent must sign and date the facsimile, and then the facsimile can serve as the original informed consent document. If facsimile is used for the informed consent document, measures must be employed to ensure the confidentiality of the information, and the privacy of the subject.

e. Copies of Signed Consent Form

(1) A copy of the signed and dated informed consent form must be provided to the subject or the subject's LAR (38 CFR 16.117(a)).

(2) Where applicable, a copy of the signed and dated informed consent form must be placed in the medical record in accordance with VHA Handbook 1907.01.

(3) The Investigator must ensure that the person who administered the consent process enters a Research Consent Note in CPRS. Note: The Investigator must also ensure that the medical record is flagged with a Research Study Participant note (Clinical Warning) if required by the IRB.

See SOP RI 803 for additional details regarding CPRS documentation.

1.6 Cognitively Impaired Subjects

Studies involving subjects who are decisionally-impaired may take place over extended periods. The IRB should consider whether periodic re-consenting of individuals should be required to ensure that a subject's continued involvement is voluntary. The IRB may require that Investigators re-consent subjects after taking into account the study's anticipated length and the condition of the individuals to be included (e.g., subjects with progressive neurological disorders). Additionally, the IRB should consider whether, and when, it should require a reassessment of decision-making capacity.

1.7 Waiver of Documentation

Per 38 CFR 16.117 (c) and 45 CFR 46.117 (c), unless the research is FDA-regulated, the IRB may waive the requirement for the Investigator to obtain a signed consent form for some or all subjects if the IRB finds either:

1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality (Note: When the IRB waives the requirement for documentation under this condition, each subject must be asked whether or not the subject wants documentation linking the subject with the research, and the subject's wishes will govern); or
2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the Investigator to provide subjects with a written statement regarding the research.

If the Durham VAHCS IRB approves a waiver of documented informed consent, the following conditions apply:

1) The Investigator or designee must provide an adequate informed consent process regardless of whether the or not a waiver of documented informed consent has been approved.
2) The Investigator must submit a script of the language that will be presented to the subject when the study is explained.
3) A waiver of HIPAA Authorization must also be requested from the IRB.
4) The Investigator must also ensure that a research consent note documenting the subject's agreement to participate is placed in CPRS. The note must document the process by which consent was obtained in the 'Other' section of the research consent note template (e.g., waiver of documented consent). The research consent note is not required if the waiver was approved secondary to a potential breach of confidentiality.
5) The IRB's decision to waive documentation of informed consent will be captured in the minutes, along with the reason(s) why the waiver of documented informed consent was granted.

1.8 Use of Facsimile or Mail to Document Informed Consent

The IRB may approve a process that allows the informed consent document to be delivered by mail or facsimile to the potential subject or the potential subject's legally authorized representative and to conduct the consent interview by telephone when the subject or the legally authorized representative can read the consent document as it is discussed. All other applicable conditions for documentation of informed consent must also be met when using this procedure.

2. Scope

These policies and procedures apply to all research submitted to the IRB.

3. Responsibility

Investigators are responsible for creating and maintaining appropriate informed consent documents.

IRB Program Administrator and/or staff are responsible for reviewing all incoming informed consent documents and for communicating with Investigators to bring documents into compliance.

IC 702: WAIVER OF INFORMED CONSENT

1. Policy

The IRB may approve a consent procedure that does not include, or which alters, some or all of the elements of informed consent (such as written documentation). The IRB may waive the requirement to obtain informed consent if the IRB finds that the research meets specific criteria.

For research subject to Department of Defense (DoD) regulations, if the research subject meets the definition of "experimental subject," policies and procedures prohibit a waiver of the consent process unless a waiver is obtained from the Secretary of Defense. If the research subject does not meet the definition of "experimental subject," the IRB is allowed to waive the consent process. Note: See Glossary for definition of "experimental subject."

Also for research subject to DoD regulations, an exception from consent in emergency medicine research is prohibited unless a waiver is obtained from the Secretary of Defense.

1.1 IRB Waives One or More Requirements of Informed Consent

Per 38 CFR 16.116(c) and 45 CFR 46.116 (c), unless the research is FDA-regulated, the IRB may approve a consent procedure that does not include, or which alters, some or all of the elements of informed consent (see SOP IC 701), or waive the requirement to obtain informed consent provided the IRB finds and documents that:

A. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

   Public benefit or service programs;

   Procedures for obtaining benefits or services under those programs;

   Possible changes in or alternatives to those programs or procedures; or

   Possible changes in methods or levels of payment for benefits or services under those programs; and

B. Unless FDA-regulated, the research could not practicably be carried out without the waiver or alteration.

   Or

Unless the research is FDA-regulated, an 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 the IRB finds and documents that:

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

If the IRB disapproves the waiver for informed consent request, the Investigator must submit an informed consent form for IRB approval and seek prospective consent from research subjects.

The IRB's decision to waive the informed consent process will be captured in the minutes, along with the reason(s) why the waiver for consent was granted.

1.2 The IRB Waives the Requirement to Obtain Documentation of Consent

For information regarding waivers of documented informed consent, see SOP IC 701, Section 1.7.

1.3 An Emergency Situation Prior to IRB Review and Approval

Obtaining informed consent shall be deemed feasible except in certain emergency situations where the Investigator has adequately documented the necessary exception under the guidelines described in 21 CFR 50.23 and 45 CFR 16.116, and in SOP SC 502, section 1.3.

Time was not sufficient to obtain consent from the subject or the subject's legal representative.

The Durham VAHCS does not conduct planned emergency research subject to 21 CFR 50.24 – Exception from Informed Consent Requirements for Emergency Research.

2. Scope

These policies and procedures apply to all research submitted to the IRB.

3. Responsibility

IRB, IRB Chairperson (or designee) is responsible for determining whether informed consent waivers are applicable and appropriate and for follow-up with Investigators as indicated from the waiver assessment.

IC 703: SURROGATE CONSENT AND ASSENT

1. Policy

The principle of respect for persons requires that the choice of an autonomous person be respected. Under the usual conditions of clinical research, this is accomplished by soliciting the informed consent of the prospective research subject. In the case of the cognitively impaired adult or non-autonomous child, applying the principle of respect for persons is problematic. Therefore, consent of either the parent or legally authorized representative is required (i.e., surrogate consent). However, any individual capable of some degree of understanding (generally, a child of seven or older, or a cognitively impaired adult) should participate in research only if they assent. When assent is required by the IRB, however, the decision of the individual assenting should be binding.

1.1 Assessment of Capacity

Before persons who lack decision-making capacity may be considered for participation in any VA research, the IRB must find that the proposed research meets all of the conditions contained in SOP SC 501.

1.2 Investigators' Responsibilities for Surrogate Consent

When the potential subject is determined to lack decision-making capacity, investigators must obtain consent form the LAR of the subject (i.e., surrogate consent). Investigators must provide the IRB with a description of the procedures to ensure that subjects' LARs are well informed regarding their roles and obligations to protect persons who lack decision-making capacity and provide information (i.e., informed consent process and HIPAA authorization) to the subjects' LARs that would ordinarily be required to be made to the subjects themselves if they had decision-making capacity.

1.3 Legally Authorized Representatives (LARs)

1.3.1 Authorized Person

The following persons are authorized to consent on behalf of persons who lack decision-making capacity in the following order of priority (38 CFR 17.32(e)):

(a) Health care agent (i.e., an individual named by the individual in a Durable Power of Attorney for Health Care (38 CFR.17.32(a)(iii));
(b) Legal guardian or special guardian;
(c) Next of kin in this order: a close relative of the patient 18 years of age or older, in the following priority: spouse, child, parent, sibling, grandparent, or grandchild; or
(d) Close friend.

NOTE: An individual who is qualified as a LAR to provide informed consent on behalf of a prospective research subject may not always qualify as a personal representative for purposes of consent to use or disclose a human subject's PHI (i.e., signing a HIPAA authorization). Therefore, in circumstances involving authorization for use or disclosure of a human subject's PHI, the Investigator must ensure the LAR meets the requirements of a personal representative (legal guardian or power of attorney) in HIPAA and the Privacy Act of 1974 prior to the LAR's signing a HIPAA authorization.

1.3.2 Responsibilities of LARs

LARs act on behalf of the potential subjects, therefore:

(a) LARs must be told that their obligation is to try to determine what the subject would do if able to make an informed decision.

(b) If the potential subject's wishes cannot be determined, the LARs must be told they are responsible for determining what is in the subjects' best interests.

(c) LARs generally assume the same rights and responsibilities as the individuals who lack decision-making capacity in the informed consent process (see 38 CFR 17.32(e)).

1.4 Dissent or Assent

If feasible, the Investigator must explain the proposed research to the prospective research subject even when the surrogate gives consent. Although unable to provide informed consent, some persons may resist participating in a research (i.e., if they dissent) protocol approved by their representatives. Under no circumstances may a subject be forced or coerced to participate in a research study even if the LAR has provided consent.

1.4.1 Use of Assent

Assent means a subject's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

In determining whether subjects are capable of assenting, the Investigator and the IRB shall take into account the age, maturity, and psychological state of the subject 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. If the IRB determines that the capability of some or all of the subjects is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the subject and is available only in the context of the research, the assent of the subject is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived as stated in SOP IC 702.

When the Investigator request approval from the IRB to include persons in the research who lack the ability to provide consent, the IRB must evaluate:

- whether the plan for the assessment of the capacity to consent is adequate,
- whether assent of the participant is a requirement, and if so,
- whether the plan for assent is adequate.

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

1.5 Fluctuating Capacity

Investigators, IRB members, and LARs must be aware that decision-making capacity may fluctuate in some subjects. 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.

2. Scope

These policies and procedures apply to all research submitted to the IRB.

3. Responsibility

IRB Chairperson (or designee) is responsible for determining whether assent is indicted and for follow-up with Investigators, as appropriate.

IC 704: PRIVACY RULE AND RESEARCH

1. Policy

The Privacy Rule of 2000 establishes minimum standards for protecting the privacy of individually identifiable health information. It establishes conditions under which the covered entity can provide researchers access to and use of protected health information when necessary to conduct research. The Privacy Rule recognizes that the research community has valid reasons to use, access, and disclose individually identifiable health information to carry out a wide range of health research protocols and projects. In the course of conducting research, researchers may create, use, and/or disclose individually identifiable health information. The Privacy Rule protects the privacy of such information when held by a covered entity but also provides various ways in which researchers can access and use the information for research.

The Investigator shall obtain from individual research participants authorization to use or disclose their individually identifiable health information as required by the Health Insurance Portability and Accountability Act (HIPAA Privacy Rule) prior to the start of research. Research Investigators may also seek access through one of the four alternative methods: (1) waiver of authorization, (2) limited data set which requires a data use agreement with the recipient of the information, (3) decedent's research, or (4) preparatory to research.

A written HIPAA authorization signed by the individual to whom the information or record pertains is required when VA health care facilities need to access, collect, develop, use, or disclose individual-identifiable health information for a purpose other than treatment, payment, or health care operations (e.g., research) unless there is legal authority (e.g., waiver, limited data set with data use agreement, etc.) to disclose such information. Authorization for a use or disclosure of psychotherapy notes is not combined with any other authorization for use or disclosure unless the other authorization is also for a use or disclosure of psychotherapy notes.

The Durham IRB must approve the use of PHI for all proposed research, but cannot approve a HIPAA authorization document. The Privacy Officer must review the HIPAA authorization to ensure it contains all required elements and is consistent with all privacy requirements before the PI can begin to use or collect the individual's information based on an approved research protocol. All Investigators conducting human subjects' research at the Durham VAHCS must obtain authorization from the potential participants to use and disclose PHI. The IRB has the authority at the Durham VAHCS to grant a waiver of authorization or one of the alternatives.

Data disclosed under a properly executed HIPAA authorization must be securely transferred according to VA information security requirements.

1.1 Authorization

When obtaining informed consent from prospective research subjects with an approved informed consent form, Investigators must obtain permission, in the form of an Authorization, from the individual to use and/or disclose PHI in conjunction with the research study. If the individual refuses to sign the authorization at the time of consent he/she will not be allowed to sign consent to participate in the research study. Investigators are provided a stand-alone research-specific authorization document (VA Form 10-0493) that is separate from the informed consent document. Investigators must use the authorization form provided and make it study-specific.

Authorizations must describe:

- The health information + identifiers[1]
- Who may use or disclose the information
- Who may receive the information
- Purpose of the use or disclosure (must be limited to the specific research study)
- Expiration date or event (can state "none")
- Individual's signature and date
- Right to revoke authorization (permits continued use/disclosure to maintain integrity of research study)
- Inability to condition enrollment, treatment, payment, or eligibility for benefits (except for research related treatment)
- Re-disclosures may no longer be protected by the Rule

The researcher must provide the participant with a copy of the signed Authorization form.

A valid and properly executed HIPAA authorization is permission from the subject for the covered entity (VA) to use/and or disclose the subject's protected health information. A HIPAA authorization is different from a subject's informed consent. A HIPAA authorization, when executed, is the subject's permission for his/her identifiable health information to be used and/or disclosed for a research purpose. An informed consent document, on the other hand, informs potential subjects of the possible risks and benefits associated with the research study and when executed indicates their willingness to participate.

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[1] Identifiers: (1)names, (2)all geographical subdivisions smaller than a state, (3)dates, (4)telephone numbers, (5)fax numbers, (6)electronic mail addresses, (7)social security numbers, (8)medical record numbers, (9)health plan beneficiary numbers, (10)account numbers, (11)certificate/license numbers, (12)vehicle identification numbers, (13)device identification numbers, (14)URLs, (15)internet protocol address numbers, (16)biometric identifiers (voice/finger prints), (17)full face photography, other (18)unique identifiers or code numbers.

1.2 Waiver of Authorization

For some types of research, it is impracticable for researchers to obtain written authorization from the participants. A researcher must seek a waiver of authorization from the IRB every time he/she wants to access Protected Health Information (PHI) for research purposes without a signed authorization from the participant**.** To obtain the waiver, the researcher must provide adequate justification to the IRB to allow the IRB to make its determination. The researcher must submit to the IRB details of his or her request and applicable justification. A researcher must also request a waiver of authorization from the IRB when writing or recording individually identifiable health information or other identifiable private information for the purpose of screening and/or recruiting potential subjects for research. This type of waiver is often referred as a "partial waiver", meaning a signed Authorization is required from the participant at the time of enrollment. A Waiver of Authorization requires prospective IRB approval and there are three criteria that must be satisfied.

- An adequate plan to protect the identifiers from improper use/disclosure
- An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining identifiers or such retention is otherwise required by law
- Adequate written assurances that PHI will not be reuse/disclosed to any other person or entity, except as required by law

1.2.1 IRB Documentation

The IRB must document its findings in the IRB minutes or the IRB protocol file. If IRB does not document the waiver of authorization as required, the waiver is not valid. Documentation must include, but is not limited to, all of the following:

(1) Identification of the IRB of record.

(2) Date of IRB approval of waiver of HIPAA authorization.

(3) Statement that the waiver of HIPAA authorization satisfies the following criteria:

(a) The use or disclosure of the requested information involves no more than minimal risk to the privacy of individuals based on, at least, the presence of the following elements:

1. An adequate plan to protect the identifiers from improper use and disclosure;

2. An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise mandated by applicable VA or other Federal requirements; and

3. Adequate written assurances that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the Privacy Rule.

(b) The research could not practicably be conducted without the waiver; and

(c) The research could not practicably be conducted without access to and use of the requested information.

(4) A brief description of the PHI for which the IRB has determined use or disclosure to be necessary.

(5) The specific findings on which the IRB based its decision to grant the waiver of HIPAA authorization.

(6) Identification of the IRB review procedure used to approve the waiver of HIPAA authorization (either convened IRB review procedures (see par. 13 and 38 CFR 16.108(b) or expedited review procedures (see par. 21 and 38 CFR 16.110).

(7) Signature of Chair of the IRB, or qualified voting member of the IRB designated by the Chair, on the HIPAA authorization waiver document. Note: Signatures may be electronic if they meet VA requirements for electronic signatures.

1.3 Limited Data Set

A limited data set is another option researchers can use to access PHI for the purpose of research. A limited data set is a set of data that are not fully de-identified. A covered entity may use or disclose a limited data set without an authorization for the purpose of research if they enter into a “data use agreement” with the recipient of the data. The recipient of the data must agree to a “data use agreement” that generally describes the permitted uses and disclosures of the information received and prohibits re-identifying or using this information to contact individuals. A limited data set is PHI that excludes specified direct identifiers of the individual or of relatives, employers, or household members of the individual. Of the 18 identifiers, a researcher can retain:

- Dates
- Geographic information (but not street address)
- Other unique identifying numbers, characteristics, or codes that are not expressly excluded

Researchers are not required to track disclosures when using a limited data set. Researchers are required to make all reasonable efforts to limit disclosures of PHI to the minimum amount necessary to accomplish the intended purpose of the PHI use, disclosure or request when using a limited data set.

1.4 Decedent Research

Researchers may use and disclose PHI without an authorization for research on decedents. Decedents are afforded the same privacy protections as the living under HIPAA. It requires a notification to the IRB of the intent to do decedents' research. The Durham VAHCS is also free to impose additional restrictions on access to information about decedents. The researcher must notify the Durham VAHCS IRB in writing of the intent to conduct decedent's research and submit sufficient information to document that the PHI is the minimum necessary for research purposes and that the PHI will be used solely for the purpose of research. The Durham VAHCS may request that the research submit documentation of death. The requirements on the Investigator are:

- Representation that the use or disclosure sought is solely for research on the protected health information of decedents;
- Documentation, at the request of the covered entity, of the death of such individuals; and
- Representation that the protected health information for which use or disclosure is sought is necessary for the research purposes.

1.5 Preparatory to Research

Data repositories (including VA medical records) may be used by VA Investigators for activities that are preparatory to VA research without the requirement to obtain either a HIPAA authorization from the subject or waiver of HIPAA authorization by an IRB or Privacy Board. This includes use of PHI for the preparation of a research protocol prior to submission to the IRB. "Preparatory to research" activity is the only instance of access for research purposes allowed in VHA without a written HIPAA authorization signed by the individual, a waiver of HIPAA authorization by an IRB or Privacy Board, or approval by the IRB.

(1) VA Investigators must not arbitrarily review PHI based on their employee access to PHI until the Investigator documents the following required information as "Preparatory to Research" in a designated file that is readily accessible for those required to audit such information (e.g., Health Information Manager, Privacy Officer, or other designated individual):

a) The access to PHI is only to prepare a protocol;
b) No PHI will be removed from the covered entity (i.e., VHA); and
c) Access to PHI is necessary for preparation of the research protocol.

(2) Non-VA researchers may not obtain VA information for preparatory to research activities without appropriate VA approvals.

(3) During the preparatory to research activities the VA Investigator:
   a) Must only record aggregate data. The aggregate data may be used only for background information, to justify the research, or to show that there are adequate numbers of potential subjects to allow the Investigator to meet enrollment targets or sample size requirements.
   b) Must not record any individually identifiable health information; and
   c) Must not use any individually identifiable information to recruit subjects.

Note: Preparatory activities can include reviewing database output (computer file or printout) containing identifiable health information generated by the database owner, if the investigator returns the database output to the database owner when finished aggregating the information.

(4) Contacting potential research subjects and conducting pilot or feasibility studies are not considered activities preparatory to research.

(5) Activities preparatory to research only encompass the time to prepare the protocol and ends when the protocol is submitted to the IRB.

1.6 Revocation of Authorization

A research subject must revoke his/her authorization to use and/or disclose PHI for research purposes in writing. If the individual has not previously done so, ask that he/she submit the request in writing. The researcher can provide a copy of the *VA Form 10-10116, Revocation of Authorization for Use and Release of Individually Identifiable Health Information for Veterans Health Administration (VHA) Research.*

The date that the written revocation is received from the individual is the day that his/her PHI may no longer be use/disclosed for research purposes. However, if the PHI has already been included in an analysis, and the information is needed to maintain the integrity of the research, the PHI may still be used for that analysis.

An aggregate number of revocations must be reported to the IRB at the time of continuing review.

2. Scope

These policies and procedures apply to all research submitted to the IRB.

3. Responsibility

IRB, IRB Chairperson (or designee) is responsible for determining whether an Authorization, waiver of authorization, limited data set, or decedents' research is applicable and appropriate. Investigators are responsible for submitting sufficient information to the research office concerning these activities.

RI 801: INVESTIGATOR RESPONSIBILITIES

1. Policy

The Investigator is responsible for personally conducting and supervising all study-related activities. The Investigator must give first priority to the protection of research subjects. The Investigator must hold a current VA appointment to conduct VA research. Investigators and co-Investigators must be identified on the IRB application and must provide credentials, conflict of interest statements or other documentation required by VA and local facility policies.

1.1 Investigator Responsibilities

The PI, LSI, and Investigator must uphold professional and ethical standards and practices and adhere to all applicable VA and other Federal requirements, including the local VA facility's SOPs, regarding the conduct of research and the protection of human subjects. The responsibilities of the Investigator may be defined in the protocol or IRB application. Specifically, the PI's and LSI's responsibilities include, but are not limited to: ***NOTE:*** *Some of the following responsibilities may be assumed by an Investigator working under a PI or LSI.*

O. Disclosing Conflicts of Interest: This means disclosing to the IRB any potential, actual, apparent, or perceived conflict of interest of a financial, professional, or personal nature that may affect any aspect of the research, and complying with all applicable VA and other Federal requirements regarding conflict of interest.

P. Ensuring Adequate Resources: This means ensuring there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient Investigator time, appropriately qualified research team members, equipment, and space.

Q. Ensuring Qualified Research Staff: This means ensuring research staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials and, when relevant, privileges) to perform procedures assigned to them during the study. In a protocol, study team members are generally identified by name or by title.

(1) If a study team member is identified by name in the IRB-approved protocol, a replacement or termination of their role constitutes a change in the protocol. Such a change requires IRB approval (e.g., if an IRB-approved protocol specifically identified the name of a medical monitor and later another individual was identified to replace the medical monitor, the protocol would require an amendment reflecting the change in the name of the medical

monitor. This protocol change would require IRB approval prior to initiation of the change, unless it was necessary to eliminate apparent immediate hazards to the subjects).

(2) If a study team member is replaced by another individual and the IRB-approved protocol identifies the person by title and not name, a replacement by another individual with the same title is not a protocol change. No IRB approval is required (e.g., if a PI appointed a new research study coordinator to replace the original research study coordinator in an IRB-approved protocol when neither is mentioned by name, the replacement in personnel does not require approval by IRB because the protocol remains unchanged).

The IRB may also require a specific individual(s) by name to be part of the study team as a condition for IRB approval of the research. In that case, a proposed change in that specific individual would require IRB approval.

The Investigator must be appropriately trained and credentialed to conduct research involving human subjects by a program that meets all VA requirements. Non-physicians conducting research involving the use of pharmaceutical agents must have a physician identified (co-Investigator or consultant) to write prescriptions and follow potential drug interactions.

R. Promptly Reporting Changes in PI or LSI: This means promptly reporting any changes in the PI or LSI to the IRB. Changes in other key research staff, if any, must be reported at time of the change or continuing review, whichever occurs first. These changes include, but are not limited to, additions to or loss of staff. Changes in the PI, LSI, Co-PI, or Co-LSI of an IRB-approved project must be evaluated and approved by IRB to ensure the new individual meets the criteria described in 38 CFR 16.111.

S. Overseeing Research Staff: This means overseeing and being responsible for ensuring the research staff under the Investigator's direction comply with all applicable requirements including, but not limited to, implementing the research study in accordance with the approved protocol.

The Investigator is ultimately responsible for the conduct of the trial and all actions of the Study Team. Over-delegation and inadequate supervision by the Investigator can lead to serious problems in the trial and is a continuing concern of the FDA, the VA, and other Sponsors of clinical research. If the Investigator delegates broad responsibilities to

the Study Coordinator or other member of the Study Team, the Investigator should define in writing the scope of delegated responsibilities and should specify by name the team member authorized to perform such tasks (via a Scope of Practice document and list the individual on the study Staff Listing). This is helpful for the Study Coordinator and other members of the Study Team and ensures that everyone knows that team members are acting under explicit authority granted by the Investigator.

T. Ensuring Complete Information in Research Protocols: This means ensuring the research protocol contains all required information in SOP RI 802.

U. Obtaining Written Approvals: This means obtaining written approval(s) before initiating research. Before initiating the research study at a given site, IRB approval must be obtained in writing from the Chair or other voting member of the IRB, and all other committees (e.g., R&D Committee), subcommittees, and other approvals according to applicable local, VA, and other Federal requirements.

(1) For a VA multi-site study, not only the PI, but also <u>all</u> LSIs, must obtain such approvals from the relevant local VA facilities' IRBs of record and all other local committees, subcommittees, and other approvals according to the respective applicable local, VA and other Federal requirements.

(2) Research cannot be initiated at any given site until the local Investigator has obtained written notification that the research can be initiated from the local ACOS for R&D (see VHA Handbook 1200.01).

V. Implementing the Study as Approved: This means ensuring the study is implemented as approved by the IRB and in accordance with other required approvals and with all applicable local, VA, and other Federal requirements including, when applicable, those for research involving investigational drugs or investigational devices.

W. Maintaining Investigator's Research Records: This means maintaining written documentation on file that the protocol is being implemented as approved by IRB and in accordance with other required approvals. Research records include the following when relevant to the study:

(a) Copies of all IRB-approved versions of the protocol and amendments.

(b) Case report forms and supporting data, including, but not limited to, signed and dated informed consent forms and HIPAA authorizations.

(c) Documentation on each subject including, but not limited to: informed consent, interactions with subjects by telephone or in person, observations, interventions, and other data relevant to the research study, including, but not limited to progress notes, research study forms, surveys, and questionnaires.

(d) Reports of adverse events.

(e) Data analyses.

(f) Reports including, but not limited to, abstracts and other publications.

(g) All correspondence including, but not limited to, that with the funding source or sponsor, and with applicable oversight entities including, but not limited to, IRB, R&D Committee, ORO, and FDA.

(h) A master list of all subjects for whom informed consent has been obtained in the study.

Documents must be maintained so that they may be audited by the facility RCO or other entities according to applicable sponsor, local, VA and other Federal requirements. An Accounting of Disclosure must be maintained for each and every disclosure of information from this study to a non-VA entity. ***NOTE:*** *The facility Privacy Officer can assist in providing a mechanism to account for this disclosure.*

These are a few hints for maintaining regulatory files:

- Keep copies of all submissions to and from the IRB including attachments.
- Use cover letters to clearly identify all documents being submitted.
- Document all contacts with the IRB – “get it in writing”.
- Use tickler files/flow sheets/tracking logs.

- Request more detail in approval notices if necessary.
- Keep files organized preferably in reverse chronological order.

X. Obtaining Informed Consent: This means ensuring that no human being is involved as a subject in research covered by this Handbook unless legally effective informed consent of the subject or the subject's LAR has been obtained (38 CFR 16.116). The informed consent must be obtained and documented prospectively (i.e., no screening or other interaction or intervention involving a human subject can occur until after the IRB-approved informed consent requirements have been met). The only exceptions are if the IRB of record determines the research is exempt (see 38 CFR 16.101(b)), or approves a waiver of informed consent (see 38 CFR 16.116(c) and (d), or approves a waiver of the signed informed consent form (see 38 CFR.117(c).

Reminder: If someone other than the Investigator obtains consent, that person must be formally delegated in writing and the person delegated must have appropriate training and education to perform this activity. The Scope of Practice is an acceptable method to formally delegate this responsibility; this person must also be a member of the research team and listed on the study Staff Listing.

If the investigator contracts with a firm (e.g., a survey research firm) to obtain consent from subjects, collect private individually identifiable information from human subjects, or are involved in activities that would institutionally engage the firm in human subjects research, the firm must have its own IRB oversight of the activity. In addition, the PO must determine that there is appropriate authority to allow the disclosure of individual names and other information to the contracted firm.

The investigator must ensure that all original signed and dated informed consent documents are maintained in the investigator's research files, readily retrievable, and secure.

See SOP IC 701 for additional details on informed consent.

Y. Ensuring Consistency of Informed Consent Form, Protocol, and HIPAA Authorization: This means ensuring the language in the informed consent form is consistent with that in the protocol and, when applicable, in the HIPAA authorization.

Z. Ensuring HIPAA Authorization is Obtained: This means ensuring that no human being is involved as a subject in research unless the Investigator or a designee formally and prospectively designated in writing in the protocol by the Investigator has obtained legally effective HIPAA authorization for the use and disclosure of the subject's PHI, or has obtained Privacy Board or IRB-

approved waiver of HIPAA authorization, unless there is a limited data set and appropriate DUA.

(1) If the Investigator requires a waiver or alteration of the HIPAA authorization, the Investigator must provide the Privacy Board or IRB with information sufficient for the Privacy Board or IRB to find that such waiver or alteration is necessary.

(2) Investigators can obtain and use real Social Security numbers only when real Social Security numbers are required to meet the specific aims of the research protocol or to enter information into the subjects' health records. The collection and use of real Social Security numbers must be approved by IRB, and the Investigators must follow all applicable VA and other Federal requirements for obtaining and using real Social Security numbers.

AA. Ensure that the research and consent process is documented in the medical and research record.

(1) Ensure that the person who administered the consent process enters the Research Consent Note in CPRS.

(2) Ensure that the medical record is flagged with a Research Study Participant Note (Clinical Warning) if required by the IRB and that the 10-9012 is scanned as an attachment to the Research Study Participant Note (Clinical Warning), if applicable.

See SOP RI 803 for additional detail on CPRS documentation (i.e., Research Consent Notes and Clinical Warnings).

BB. Ensuring Proper Research Contacts for Participants: The investigator must ensure that all informed consent forms provide subjects with required contact information for the VA Investigator and relevant study staff. In addition, all informed consent forms must provide a contact independent of the research team in case the research staff cannot be reached, and the subject wish to talk to someone other than the research staff, or the subject wishes to voice concerns or complaints about the research.

The investigator is also responsible for informing the independent contact person who is independent of the research team (e.g., the facility's patient advocate, a member of the research office staff, or IRB staff) of the relevant details of the study; documenting that this independent contact person has been informed; and ensuring the

independent contact person's ability to render proper assistance to potential subjects.

CC. Ensuring Appropriate Telephone Contact with Subjects: This pertains to contacting the subject by telephone. Research team members are prohibited from requesting Social Security Numbers by telephone.

(1) Initial Contact: During the recruitment process, ensuring the research team makes initial contact with the potential subject in person or by letter prior to initiating any telephone contact, unless there is written documentation that the subject is willing to be contacted by telephone about the study in question or a specific kind of research (e.g., if the potential subject has diabetes, the subject may indicate a desire to be notified of any diabetes-related research studies). The initial contact must provide a telephone number or other means that the potential subject can use to verify the study constitutes VA research. Note: If a research repository from a previous study is used to identify subjects, there must be an IRB approved HIPAA waiver for this activity in the new protocol.

(2) If a contractor makes the initial contact by letter, the VA investigator must sign the letter.

(3) Later Contact: Ensuring the research team begins telephone calls to the subject by referring to previous contacts and, when applicable, the information provided in the informed consent form, and ensuring that the scope of telephone contacts with the subject is limited to topics outlined in IRB-approved protocols and informed consent forms.

DD. Obtaining IRB Approval for all changes: This means obtaining IRB approval for all changes to the research protocol (e.g., amendments or modifications), including changes to the IRB informed consent form (the IRB informed consent form is unique to each research study), prior to implementing the changes. The only exception is when it is necessary to change the protocol to eliminate apparent immediate hazards to the subject. The Investigator must promptly report these changes to the IRB.

EE. Submitting Continuing Review Materials: This means ensuring continuing review materials are submitted in a timely manner to provide IRB sufficient time for reviewing and approving the study before IRB approval expires.

Reminder: The length of time approval is given to a research protocol will be no more than one year, and is dependent on the risk involved with the research. IRB approval automatically expires if the continuing review and approval does not occur by the expiration date of the current approval. An IRB Request for Continuing Review of Research will be available to the Investigator for this purpose.

FF. Reporting Deviations and Complaints: This means reporting deviations from the protocol and subject complaints to IRB per SOP RR 403.

GG. Reporting to the IRB: This means reporting all unanticipated problems involving risks to subjects or others, serious unanticipated problems involving risks to subjects of others, local unanticipated SAEs, apparent serious or continuing noncompliance, any termination or suspension of research, and privacy or information security incidents related to VA research, including any inappropriate access, loss, or theft of PHI, noncompliant storage, transmission, removal, or destruction of PHI, or left, loss, or noncompliance destruction of equipment containing PHI, in accordance with local policy and VHA Handbook 1058.01.

HH. Completing Appropriate Actions at Research Project Completion: This means at completion of the research study, completing all required documentation and storing research records according to all applicable VA and federal records retention requirements. If appropriate, the Investigator communicates the results to subjects or the community from which subjects were recruited.

II. Transferring of Records: This means transferring of records by VA upon departure of the Investigator**.** If the Investigator leaves VA, all research records are retained by the VA facility where the research was conducted. If the grant is ongoing and the Investigator leaves one VA facility to go to another VA facility, the Investigator must obtain approval for a copy of relevant materials to be provided to the new VA facility's research office. The approval must be obtained from the first VA facility's research office, any other relevant individuals or offices according to VA and local requirements (e.g., compliance, privacy, or Information Security Officers (ISOs)) and the sponsor. Electronic records from closed studies and prior investigators will be maintained in file locations that allows for access to data. Where applicable (e.g., investigators are no longer at the DVAHCS), the electronic study data may be transferred to the Research Office for maintenance and retention. **Note:** The Investigator is not the grantee, nor does the Investigator own the data. Prior investigators may not remove DVAHCS research data unless there is prior written approval do so.

JJ. Maintaining a Master List of All Subjects: This means the Investigator must maintain a master list of all subjects from whom informed consent has been

obtained whether or not IRB granted a waiver of documentation of informed consent (see 38 CFR16.117(c)).

(1) Investigators must not add a subject's name to the master list of all subjects until after:

(a) Informed consent has been obtained from that subject,

(b) When appropriate, informed consent has been documented using an IRB-approved informed consent form.

Note: The IRB may waive the requirement for the Investigator to maintain a master list for a given study if both of the following conditions are met: there is a waiver of documentation of informed consent and the IRB determines that including the subjects on such a master list poses a potential risk to the subjects from a breach of confidentiality.

The Investigator must secure the master list appropriately in compliance with all VA confidentiality and information security requirements in the Investigator's file for each study.

KK. Ensuring Appropriate Research Laboratory Test Reporting: This means ensuring research laboratories not report laboratory results that are used for diagnosis, treatment, and prevention of disease in patients, unless the research laboratories are properly accredited and meet all requirements of 42 CFR 493 (see VHA Handbook 1106.01).

LL. Ensuring Requirements of Multi-site Studies: Investigators will abide by all requirements of mutli-site studies (see SOP SC 504).

1.2 Advertisements

All advertisements must be IRB approved prior to posting and distribution.

Postings of all advertisements must be limited to the bulletin boards within the Medical Center. The IRB will review the information content and mode of communication to determine that the procedures are not coercive. The IRB will review the final copy of printed advertisements to assess the relative size and type used and other visual effects. The IRB will review and approve the script for audio and video advertisements, as well as the final taped version. The IRB approves the materials to ensure advertisements are not coercive or create undue influence to the subject to participate.

Advertisements must include the word the "Research" and should be limited to information prospective enrollees need to determine their eligibility and interest:

- The name and address of the clinical Investigator or research facility;
- The purpose of the research and (in summary form) the eligibility criteria that will be used to admit subjects into the study;
- A straightforward and truthful description of the benefits to the subject for participation in the study;
- The location of the research and the person to contact for further information;
- Time or other commitment required of the subjects;
- A statement that subjects may be paid, without emphasizing the payment or the amount by such means as larger or bolder type; and
- Paper advertisements must include the IRB stamp when posted, and advertisements on the Television Information System must include the IRB protocol number.

Advertisements will be reviewed to assure that advertisements do not:

- State or imply a certainty of favorable outcome or other benefits beyond what is outlined in the informed consent document and protocol (e.g., a coupon good for a discount on the purchase price of the product once it has been approved for marketing;
- Make claims, either explicitly or implicitly, that the drug, biologic, or device is safe or effective for the purposes under investigation (for FDA regulated research);
- Make claims, either explicitly or implicitly, that the test article is known to be equivalent or superior to any other drug, biologic, or device (FDA regulated);
- Use terms such as "new treatment, " new medication," or "new drug" without explaining that the test article is investigational (FDA regulated);
- Promise "free medical treatment" when the intent is only to say subjects will not be charged for taking part in the investigation;
- Include any exculpatory language.

1.3 Investigational Drugs

To receive an investigational drug as defined by VHA Handbook 1108.04, in addition to FDA regulations for the conduct of research under an IND, the Investigator must:

(1) Obtain a letter of support from the Pharmacy Service / Research Investigational Pharmacist prior to initial IRB submission and include the letter of support with the initial request to review. In order to obtain a letter of support, the Investigator should provide the Pharmacy with a copy of the protocol and should provide additional study information as requested.

(2) Provide the Pharmacy Service / Research Investigational Pharmacist with a copy of the current signed informed consent document for each subject who receives investigational product. If applicable, copies of all re-consent documents should also be provided to the Pharmacy Service / Research Investigational Pharmacist.

(3) Provide the Pharmacy Service / Research Investigational Pharmacist with information on each subject receiving an investigational drug through the electronic medical record or other locally approved means. Documentation is to include allergies, toxicities, or adverse drug events related to the investigational drug, or the potential for interaction with other drugs, foods, or dietary supplements, i.e., herbals, nutriceuticals (see VHA Handbook 1108.04).

(4) Scan a completed VA Form 10-9012 (Investigational Drug Information Record) in the subject's medical record as soon as possible but no later than 14 days after the subject signs consent. The 10-9012 should be attached to the "Research-Study Participant" (Clinical Warning) note. If the subject is not a VA patient/does not have a record in CPRS, ensure that Pharmacy receives a paper copy of the subject's 10-9012.

(5) Ensure the local Pharmacy Service or Research Service Investigational Pharmacy receives:

a. A copy of the written approval letter signed by the ACOS/R&D that all relevant approvals have been obtained and that the study may be locally initiated;
b. A copy of the local IRB approval letter;
c. A copy of VA Form 10-9012, Investigational Drug Information Record, when applicable;
d. A copy of the current approved study protocol;
e. An Investigational Brochure, when appropriate;
f. Documentation of the IRB's continuing review approval;
g. IRB approved protocol revisions, amendments, and updates;
h. Any sponsor-provided documents relating to the storage, preparation, dispensing, and accountability of the investigational products;
i. Updates and changes to authorized prescribers after IRB approval;
j. Timely notice if clinical investigation is suspended or terminated by the IRB, R&D Committee, FDA, or other oversight group (e.g., ORO or the study sponsor); and
k. Notice of when the study is closed.

See SOP SC 502 for more information regarding studies with investigational drugs.

1.4 Investigational Devices

When an Investigator holds an IDE for investigational uses of test articles, the Investigator assumes all the responsibility of a sponsor of the clinical investigation under the IDE and has responsibilities that are found in 21 CFR 812. The Investigator's status is one of sponsor-Investigator (21 CFR 812.3). Sponsor responsibilities may be delegated to another person only by written agreement. Regulatory monitoring for clinical investigations performed by an Investigator holding an IDE will include monitoring sponsor responsibilities.

When an Investigator assumes the role and responsibilities of a sponsor-Investigator, the IRB Chair in conjunction with the Research Compliance Officer will evaluate the Investigator's knowledge (and educate if necessary) regarding FDA regulatory requirements according to 21 CFR 812.

Receipt storage, security and dispensing responsibilities of investigational devices must be addressed by the Investigator in the protocol at the time of submission and approved by the IRB. For all investigational device research approved by the Durham VAHCS, regulations found at 21 CFR 812.140 will apply.

Investigational devices must be appropriately managed to ensure they are not mixed and/or mistaken for similar approved devices. It is difficult to provide a single storage mechanism for research devices as with investigational drugs. In some cases investigational devices must be maintained in sterile supply, autoclaved or otherwise processed for implantation or use. It may be necessary for some devices to be installed, provided in a variety of sizes, or custom ordered, Because of this variability it is important for Investigators to adhere to the following procedures regarding investigational devices.

Each Investigator shall maintain the following accurate, complete, and current records relating to their participation in an investigation:

A. Records of receipt, use or disposition of a device that relate to:

1. The type and quantity of the device. The protocol and/or application should describe how the device will be managed. Including who will have access to the device and how it will be assured that investigational stock will not be used in place of approved devices for non-research patients.

2. Records should note the date(s) of delivery. Devices should only be delivered to the principal Investigator after full approval for the research has been obtained. If necessary the Investigator should work with the research office if delivery is required prior to approval for such things as installation, training, or testing. In some cases it may be necessary to

secure approval of others (Biomedical, AMMS, IRMS, others) prior to bringing the device on site.

Investigational devices should be stored (when feasible) in a separate, locked area away from approved devices and clearly marked 'CAUTION: Investigational Device – For Research Use Only'.

3. The batch number or code mark must be documented in the records when receiving shipment

4. Names of all persons who received, used, or disposed of each device. Investigational devices may only be used by an approved Investigator, or formally designated research team member, with a fully approved protocol, and with patients who have provided consent to participate.

5. Why and how many units of the device have been returned to the sponsor, repaired or otherwise disposed of. The Investigator or manufacturer should provide guidance for disposition of the unused, damaged or faulty devices and for the disposition of all stock and/or equipment at the termination of the research. Under no circumstances may devices be maintained after the conclusion of the research unless they have received full FDA approval and the Investigator has secured appropriate local approvals to maintain the device for clinical use.

See SOP SC502 for additional detail on studies involving investigational devices.

1.5 Student/Trainee-Conducted Research

Trainees (e.g., students, residents, or fellows of any procession) may serve as participants, but not PIs within a VA facility. Trainees may use VA human subjects data, or use human biological specimens that have been collected within VA for clinical, administrative, or research purposes only when:

1. The study has been approve by the local VA medical facility and IRB, if appropriate; and
2. Either they are enrolled in an institution with an educational affiliation agreement with that VA facility, or directly appointed to a VA training program that has no external institutional sponsorship (e.g., VA Advanced Fellowship. ***NOTE:*** *A waiver may be obtained from the CRADO under special circumstances.*

A VA Investigator sufficiently experienced in the area of the trainee's research interest must serve as PI and is responsible for oversight of the research and the trainee/student. The PI is responsible for ensuring the trainee/student complies with all applicable local, VA and other federal requirements.

In conducting the research, the trainee must comply with all VA and other federal and local institutional requirements, including those related to research, information security, and privacy.

If the trainee does not complete all aspects of the research prior to leaving VA, the VA PI must ensure the protocol is completed or terminated in an orderly fashion, and in accordance with all applicable local, VA, and other Federal requirements.

When the trainee leaves VA, the VA PI is responsible for ensuring all research records are retained by VA.

1.6 Tissue Banking

Human biological specimens collected under a Durham VA-approved protocol are not considered to be “banked” (stored) specimens if the specimens are used for only the specific purposes defined in the protocol and are destroyed either when the specific testing/use is completed or at the end of the protocol. If the specimens are sent to a non-VA institution for testing/use as defined in the protocol, once the specific analyses are performed, the remainder of the specimens must be destroyed or returned to the VA for destruction. If the specimens are destroyed at another institution, that institution must certify the destruction of the specimens in writing.

Specimens collected and stored for future research purposes are considered “banked” specimens. VA biospecimens may be banked or stored outside the VA with IRB, ACOS/R, and VA R&D committee approvals.

2. Scope

These policies and procedures apply to all researchers at the Durham VAHCS.

3. Responsibility

IRB Program Administrator (or equivalent), and/or Research Compliance Officer is responsible for tracking Investigator compliance with IRB requirements stipulated during the IRB’s review of the Investigator’s research.

The IRB (or IRB Chairperson or designee) is responsible for facilitating Investigator compliance with IRB requirements through his/her management of IRB deliberations, for engaging appropriate Investigator sanctions when Investigators are not in compliance with IRB requirements, and for and providing Investigators clear guidelines pertaining to that compliance through IRB communications to the Investigator.
The Investigator responsibilities include:

1. Design and implement ethical research, consistent with the three ethical principles delineated in The Belmont Report,
2. Comply with all applicable Federal, State, and local regulations that apply to human subjects research,
3. Ensure that all research involving human subjects is submitted to and approved by the IRB,
4. Comply with all applicable IRB policies, procedures, decisions, and requirements,
5. Conduct research as approved and obtain IRB approval BEFORE implementing changes,
6. Obtain informed consent in compliance with the regulations and as approved by the IRB,
7. Document informed consent in compliance with the regulations and as approved by the IRB,
8. Report progress of approved research to the IRB, as often and in the manner prescribed by the IRB,
9. Report to the IRB any injuries, adverse events, or other unanticipated problems involving risks to subjects or others, and
10. If the Investigator leaves, the original records must be retained at the Durham VAHCS. Electronic study data must be transferred to the Research Office for maintenance and retention if all investigator(s) and co-investigator(s) are no longer at the DVAHCS.

All study correspondence to the IRB must include the signature of the Principal Investigator.

RI 802: RESEARCH PROTOCOL

1. Policy

The Investigator is responsible for creating and maintaining a valid research protocol that is relevant to the health or welfare of the Veteran population. The Investigator may wish to solicit members of the community in which the research will be conducted to provide input on the research design or other aspects of the study.

For research subject to Department of Defense (DoD) regulations, the IRB considers the appointment of a research monitor 1) required for studies involving greater than minimal risk, although the IRB can require this for a portion of the research or studies involving no more than minimal risk if appropriate, 2) the independent research monitor is appointed by name, and 3) the research monitor has the authority to stop a research study in progress, remove individuals from the study, and take any steps to protect the safety and well-being of subjects until the IRB can assess the situation.

1.1 Investigator Responsibility for Drafting a Research Protocol

Investigators must:

a. Ensure research is scientifically sound and describes the research objectives, background, and methodology;

b. Ensure research compliance with all applicable local, VA, and other Federal requirements;

c. Provide a plan for just, fair, and equitable recruitment and selection of subjects. ***NOTE:*** *The requirement for a plan for just, fair and equitable recruitment and selection of subjects applies to both prospective and retrospective studies, including studies that use clinical or administrative databases or bio-specimens.*

VA believes it is critical to extend the benefits of research to all individuals, regardless of gender, race, or ethnicity, and strongly encourages its investigators to include all relevant demographic groups. For this reason, the subject population of VA research needs to reflect the demographics of the Veteran population so long as this inclusion does not compromise the scientific integrity of the research.

Special efforts must be made, when scientifically appropriate, to include women Veterans and Veterans who are members of minority groups in studies of diseases, disorders, and conditions that disproportionately affect these Veteran groups. This policy applies to all VA research activities involving human subjects, human specimens, and/or tissues. When there are insufficient numbers of Veterans to complete a study,

every effort must be made to enter non-Veteran subjects who meet the demographic profile of our Veteran Population.

d. Minimize risks to the subjects or others;

e. Describe the data and safety monitoring plan for prospective studies. This plan must include, but is not limited to, the following:

(1) What safety information will be collected including AEs and SAEs (see VHA Handbook 1058.01);
(2) How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with subjects);
(3) The frequency of data collection including when safety data collection starts;
(4) The frequency or periodicity of review of cumulative safety data;
(5) If not using a DMC, and if applicable, statistical tests for analyzing the safety data to determine if harm is occurring;
(6) Provisions for the oversight of safety data (e.g., by a DMC); and
(7) Conditions that trigger an immediate suspension of the research, if applicable.

***NOTE**: The data and safety monitoring plan may vary depending on the potential risks, complexity, and nature of the study. The use of an independent DMC needs to be considered if there are multiple clinical sites, the study is blinded, interventions are high-risk, vulnerable populations are included, or when required by the funding organization, FDA, sponsor, or other relevant entity.*

f. Describe the safety and monitoring plan for retrospective studies, including studies involving pre-existing data and biological specimens. When applicable, the plan needs to include, but is not limited to, the following:

(1) A discussion with the subject of potential study outcomes that may have an effect on the subject's health or well-being; and
(2) A procedure to determine when and how to notify individual subjects or their health care providers of findings that may affect the subjects' health.

g. Differentiate Usual Care from Research

If the protocol involves "usual care," the protocol must either include a narrative section or there must be a separate document in the IRB application that clearly differentiates the research intervention(s) from "usual care" (whether the "usual care" is limited to one "arm" of the study or is being delivered to all study subjects).

(1) When a study involves "usual care," in the protocol or a separate document in the IRB application the Investigator must clearly designate the individual or entity (e.g., the appropriate research personnel versus the subject's health care provider) responsible for relevant aspects of both the research and the usual care.

(2) The subject needs to be able to identify which activity (e.g., treatment or service) is research, and which is usual care, and know who (the researcher or the subject's health care provider) is responsible for:

(a) Explaining potential risks and benefits of the treatment or service to the subject;
(b) Providing the treatment or service;
(c) Monitoring the treatment or service, as applicable;
(d) Defining whether the adverse events result from usual care or research, as applicable;
(e) Alerting the subject if there is a problem with the treatment or service (e.g., a newly discovered risk, a product recall); and
(f) Documenting the subject's clinical course while receiving the treatment or service, as applicable.

NOTE: *The researcher and the subject's health care provider may be the same individual. If they are different individuals, and the subject's health care provider is not involved in the research study, the health care provider is not considered to be a member of the research team.*

h. Enlist Clinical Expertise
If the Investigator is not a clinician, when appropriate, the protocol must have provisions for enlisting the services of a clinician with appropriate expertise and privileges to perform duties that may include, but not be limited to: reviewing the data, adverse events, and new study findings; and making required decisions to protect the health of the subject (e.g., stopping the participant's involvement in the study or determining when to notify the subject or the subject's health care provider of information that may affect the health of the subject).

i. Provide for Privacy and Confidentiality
To facilitate review of the protocol by the Privacy Officer, the Investigator must either dedicate specific sections of the protocol to privacy and confidentiality, or the Investigator must develop an additional document that specifically addresses all privacy and confidentiality issues in the protocol; this becomes part of the IRB protocol file. The description needs to be sufficiently specific for the reader to understand how this requirement protects the subject's privacy and the confidentiality of the data. These procedures must be in compliance with all applicable VA and other federal requirements.

j. Provide for Information Security
To facilitate review of the protocol by the ISO, the Investigator must either dedicate specific sections of the protocol to information security, or the Investigator must develop an additional document that specifically addresses all information security issues in the

protocol; it becomes part of the IRB protocol file. The plan must clearly identify and include, but not be limited to:

(1) Whether or not individually identifiable information is to be collected or used;
(2) How the data is to be collected or acquired;
(3) Where the data (original and all copies) is to be stored and corresponding security systems;
(4) How the data is to be transported or transmitted from one location to another;
(5) Who is to have access to the data and how they are to access it (anyone who has access to the data is responsible for its security);
(6) All entities or individuals outside VHA to whom the data is to be disclosed, and the justification for such disclosure and the authority (e.g., the HIPAA authorization);
(7) Who is to have access and be responsible for the security of the information (e.g., the Coordinating Center, the statistician, and PI who has ultimate responsibility);
(8) Mechanisms used to account for the information;
(9) Security measures that must be in place to protect individually identifiable information if collected or used; and
(10) How and to whom a suspected or confirmed loss of VA information is to be reported.

Investigators who collect, transport, and/or store VASI in paper media outside the VAHCS must obtain written authorization prior to doing so through a complete and fully executed VAHCS Memorandum, Authorization to Use, Process, Store, or Transmit VASI Outside VHA Owned or Managed Facility. Each study team member who may transport data and/or specimens offsite must complete this Memorandum prior to doing so. ISO/PO are responsible for providing the form to investigators. After all other signatures have been obtained, the memo will be routed through the HRPP Coordinator to the ACOS/R for final review, approval and signature. At the time of IRB review of the protocol, the IRB will be notified by the ISO and/or PO if written approval to transport data or specimens off-site has not been obtained.

NOTE: *The special sections of the protocol dealing with privacy and confidentiality, and with information security, may be combined.*

k. Provide Special Safeguards
When applicable, the protocol includes a narrative section that identifies any circumstances that may warrant special safeguards to protect the rights and welfare of subjects who are likely to be vulnerable including, but not limited to, those subjects who may be susceptible to coercion or undue influence; and describes appropriate actions to provide such safeguards.

l. Provide for Reuse of Data

If the data may be reused in other studies, the protocol must describe the research data repository in which the data is to be stored (see VHA Handbook 1200.12). There must be a research informed consent and a HIPAA authorization associated with the protocol unless these requirements are waived by the IRB. If the IRB does not waive the requirements then the informed consent and HIPAA authorization content must include language on the uses and disclosures of the data as defined in the protocol as well as information on how privacy and confidentiality will be maintained and how the data will be secured. If the creation and operation of the data repository is not included in the data collection protocol, there must be a separate IRB-approved protocol for the creation and operation of the data repository (see VHA Handbook 1200.12).

2. Scope

These policies and procedures apply to all Investigators at the Durham VAHCS.

3. Responsibility

The Investigator is responsible for creating and maintaining a valid research protocol.

RI 803: RESEARCH RECORDS AND DOCUMENTATION OF RESEARCH

1. Policy

A VHA health record must be created or updated, and a progress note created, for all research subjects (Veterans or Non-Veterans) who are admitted to VA facilities as in-patients, treated as outpatients at VA facilities, or when research procedures or interventions are used in or may impact the medical care of the VA research subject at a VA facility or at facilities contracted by VA to provide services to Veterans (e.g., contract CBOCs or contract nursing homes) (see VHA Handbook 1907.01). Informed consent documents are not required to be in the health record.

1.1 VHA Health Record

A record must be created when the research requires use of any clinical resources, such as: radiology, cardiology (e.g., electrocardiogram, stress test, etc.), clinical laboratory, and pharmacy; or if the research intervention may lead to physical or psychological AEs (see VHA Handbook 1907.01).

For Veterans participating in research at the Durham , VAHCS this will be documented by a Research Consent Note in the Computerized Patient Record System (CPRS). Non-Veterans must have similar documentation created and kept in a research record maintained by the Principal Investigator.

1.2 Research Consent Notes

The research team member (Principal Investigator, Study Coordinator, etc.) who administered the informed consent process must enter a Research Consent Note in CPRS within 24 hours of the subject providing informed consent and/or signing the informed consent form. At a minimum, the Research Consent Note must include the following information for an approved research study:

- The name of the study;
- The name and contact information of the PI;
- The date subject or the subject's LAR signed consent to participate;
- The name and title of the person obtaining the subject's informed consent;
- A statement that the subject or the subject's LAR was capable of understanding the informed consent process;
- A statement that the study was explained to the subject or the subject's LAR;
- A statement that the subject or the subject's LAR consented before participation in the study began;
- A statement that the subject or the subject's LAR was given the opportunity to ask questions;
- A statement that a copy of the signed and dated research informed consent form was provided to the subject or the subject's LAR.

1.3 Research-Study Participant Notes (Clinical Warnings)

Depending on the specifics of the research study, the IRB may determine that the research requires a flag in CPRS documenting a subject's participation in a research study. This flag is placed in CPRS by entering a Research-Study Participant Note, which triggers a Clinical Warning in the Crisis, Warnings, Allergies and/or Adverse Reactions, and Directives (CWAD) alerts in CPRS. This Clinical Warning is assigned to the "Postings" section on the cover page of the patient's medical record in CPRS and alerts providers that a patient is enrolled in a research study.

If applicable, the Investigational Drug Information Record (VA Form 10-9012) should be scanned and attached to the Research-Study Participant Note as soon as possible but no later than 14 days after the subject signs consent.

The purpose of the flag is to protect the subject's safety while on a protocol, alert hospital staff of a patient's participation on a research protocol, electronically flag the medical record of the patient's participation, and provide a source for more information about the study.

The IRB will notify the Investigator at time of initial review when the research requires a mandatory Clinical Warning. The IRB may require that the patient's health record be flagged if the subject's participation in the study involves:

- Any invasive research procedure (e.g., muscle biopsy or bronchoscopy);
- Interventions that will be used in the medical care of the subject, or that could interfere with other care the subject is receiving or may receive (e.g., administration of a medication, treatment, or use of an investigational device);
- Clinical services that will be used in the medical care of the subject (e.g., orders for laboratory tests or x-rays ordered as a part of the study), or that could interfere with other care the subject is receiving or may receive; or
- The use of a survey or questionnaire that may provoke undue stress or anxiety unless the IRB determines that mandatory flagging is not in the best interests of the subject (e.g., an interview study of victims of sexual assault).
- Other situations where the IRB deems necessary.

In general, the IRB will not require a Clinical Warning if:

- participation only involves one encounter, or
- participation only involves the use of a questionnaire, or
- participation only involves the use of previously collected data or biological specimens, or
- identification of the subject in a study (if the study is not greater than minimal risk) would place the subject at greater than minimal risk due to potential harm resulting from breach of confidentiality.

If the IRB determines and documents that the patient health record must be flagged in CPRS as participating in research, then the health record must identify the investigator, as well as contact information for a member of the research team that would be available at all times, and contain information on the research study or identify where this information is available. The duration of flagging is determined by local policy.

1.3.1 Entering Research-Study Participant Notes (Clinical Warnings)

A Research-Study Participant Note must be entered in CPRS within 24 hours of subject entering the study (i.e., within 24 hours of learning that a subject meets study eligibility criteria or randomization, etc.). However, in some situations the IRB may require that the Investigator enter the Research-Study Participant Note prior to a subject's entry (i.e., randomization) into a study.

At a minimum, the Research-Study Participant Note (Clinical Warning) must include the following information for an approved research study:

- The name of the study;
- The name and contact information of the PI;
- The name and contact information of the Study Coordinator;
- Brief description of the study;
- Brief description of possible adverse reactions; and
- Information on possible drug interactions and/or toxicity of the pharmaceutical agents that are being administered to the subject because of the research (i.e., investigational drugs)

1.3.2 Removing Research-Study Participant Notes (Clinical Warnings)

Once the flag (Clinical Warning) is no longer applicable, it must be removed from the Postings section of CPRS by changing the title to Research-Prior Study Participant in VistA. The flag is considered no longer applicable when:

- the study is complete;
- a subject withdraws consent;
- the Investigator withdraws/drops the subject with no plans to resume enrollment;
- the subject is in follow-up and has completed all study interventions and enrollment in a second study is no longer a risk to the subject (not applicable for FDA regulated research); or
- it is no longer necessary to alert others of a patient's participation in a study.

1.4 Progress Notes

An Investigator is required to enter research Progress Notes in CPRS if the study generates any research results that are used for medical care. Clinic visits and inpatient care for research purposes must be coded as non-billing events (see VHA Handbook 1907.01).

1.5 Research Consults

Initiating a consult for research inclusion is considered a form or recruitment for research. Investigators must have IRB approval prior to instituting research consults. The content of the consult must be submitted to the IRB for review and approval. All consults must include the IRB protocol number.

1.6 Research Records

All written information given to subjects must be in the investigator's research file along with the consent form(s). Research records will be maintained and destroyed according to the National Archives and Records Administration and VHA's Records Control Schedule (RCS 10-1). Records destruction, when authorized, will be accomplished using the then current requirements for the secure disposal of paper and electronic records. Records will not be destroyed without pre-notification to the facility records manager.

2. Scope

These policies and procedures apply to all human subject research at the Durham . VAHCS

3. Responsibility

The Investigator is responsible for creating and maintaining appropriate research records.

The IRB must determine when a patient health record must be flagged to protect the subject's safety by indicating the subject's participation in the study.

QA 901: QUALITY ASSURANCE/CONTINUOUS QUALITY IMPROVEMENT PROGRAM

1. Policy

The Durham VAHCS evaluates the Human Research Protections Program's (HRPP) effectiveness and conducts quality improvement activities. Evaluation and improvement include measuring, assessing, and improving compliance with institutional HRPP policies, assurances and other requirements for the protection of human participants in research. Quality assurance and control of the research operations ensure effective support of the IRB's mandate, and increase the quality, performance, and efficiency of the Durham VAHCS's HRPP. The CQI Program is designed to ensure compliance with local policies, federal, and state regulations. The Durham VAHCS QA/CQI program consists of three components: quality assurance, quality improvement, and continuous quality improvement. The QA/CQI program is evaluated through training and continuing education or IRB and research staff, and regular review and assessment of procedures.

1.1 Evaluation of the HRPP

The institution evaluates HRPP effectiveness and conducts quality improvement activities to continuously measure, assess and improve compliance with institutional HRPP policies and practices to protect human research subjects. The institution annually evaluates Investigator and research pharmacy compliance with the following HRPP and IRB requirements:

The institution monitors the performance of Investigators to ensure compliance with the following HRPP and IRB requirements:

A. Adherence to HRPP policies.

1. Using only IRB-approved advertisements and subject recruitment materials.
2. Conducting the consent process under circumstances that provide the subjects or authorized representative sufficient opportunity to consider participation and which minimize the possibility of coercion or undue influence.
3. Obtaining IRB approval prior to initiating changes to the protocol or consent form, except where necessary to eliminate apparent immediate hazards to participants.
4. Reporting all problems and/or events to the IRB.
5. Reporting all protocol deviations.
6. Adherence to IRB approved protocols and conditions.
7. Notifying the participants about changes to the research that might affect their willingness to continue in the study.

8. Conducting only IRB-approved research.

B. The institution monitors the performance of Investigators in implementing informed consent requirements. The institution evaluates the following via the Research Compliance Officer's (RCO) informed consent audits:

1. Obtaining consent prior to initiating any research related procedures.
2. Obtaining consent only by trained and authorized individuals.
3. Using only IRB-approved consent forms.
4. Ensuring that the consent form is appropriately signed and dated by the signer.
5. Documenting consent in the computerized record system (CPRS).
6. Providing a copy of the consent form to the participant or legally authorized representative.
7. Maintaining the original signed consent form in the case history.
8. Flagging CPRS with a Clinical Warning for research participation (as appropriate).

Additionally, Investigator's research performance is monitored via triennial regulatory audits performed by the RCO:

9. Ensuring that Investigator's research files contain all appropriate approval letters (e.g., initial amendment, continuing review) and current and archived study documents (e.g., including but not limited to the protocol, ICF, HIPAA authorization, Investigator Brochure, staff listing, pharmacy accountability documentation, 10-9012 etc.)

10. Ensuring that research staff have Scope of Practice documents and documentation of research-required training (e.g., CITI)

11. Maintaining source documentation to permit:

a) Verification of inclusion and exclusion criteria,

b) Verification that informed consent occurred prior to the start of study procedures, and

c) Review of adverse events that are determined to be Serious, Unanticipated and Related to the research.

Investigators receive notification in writing of the impending audit prior to the actual audit. The Investigator is provided a list of items to be monitored, and given the option of rescheduling if there is a conflict with the date (if applicable). Investigators and/or the research coordinator are to be available during the audit in the case of

questions. At the conclusion of the audit, the Investigator and/or research team are briefed on the findings. The Investigator is informed that he/she will receive a written report and a copy of the report will be submitted to the IRB.

C. The institution and/or the RCO monitors the IRB's adherence to federal, state, VA, local, and NIH regulations (when applicable), for (but not limited to) the following:

1. Items reviewed
2. IRB actions
3. Quorum
4. Conflict of Interest
5. Informed Consent Requirements
6. Waiver and documentation of waiver of informed consent requirements
7. Expedited review requirements
8. Exemption from continuing IRB review requirements

D. The institution and/or the RCO monitors the pharmacy's adherence to the following research requirements:

1. Receipt, storage, security, dispensing and disposition of unused stock.
2. Maintenance of an investigational drug log as outlined in VHA Handbook 1108.04.
3. Assurance that investigational drugs are not dispensed without access to the research protocol, consent form, and VA Form 10-9012.

E. The institution monitors its responsiveness to questions, concerns and complaints:

1. Timeliness of responses to questions and complaints.
2. Satisfaction with responses.

F. If gaps in performance are identified through any of the monitoring activities or other sources, the institution will implement corrective action (e.g., change policy, procedure, communication, implement education or other such intervention) to improve.

G. If gaps in performance are identified and corrective action implemented, the institution reassesses performance to assess the effectiveness of the action taken.

H. The institution tracks the following Quality Improvement (QI) factors:

1. Identified need for improvement,

2. Action taken to improve,
3. Results of QI activities including pre- and post- evaluation measurement.

I. The facility Director is responsible for ensuring that the Facility Director's Certification of Research Oversight is completed annually.

2. Scope

These policies and procedures apply to the HRPP; specifically, the IRB, the pharmacy responsible for controlling clinical trials materials, and all Investigators conducting human subjects research reviewed and approved by the Durham VA M C IRB and Research and Development committees.

3. Responsibility

The MCD is responsible for ensuring an annual evaluation of the Durham VAHCS HRPP.

The ACOS/R&D, HRPP Coordinator, and Research Compliance Officer is responsible for the establishment, implementation and oversight of the QA/QC program.

The Durham VAHCS and IRB have the authority to implement a QA/CQI program and to act on identified deficiencies by implementing corrective action via revisions to the Standard Operating Policies and Procedures.

QA 902: AUDITS BY REGULATORY AGENCIES

1. Policy

The Durham VAHCS acknowledges that certain regulatory agencies have the authority to audit the operations of IRBs, and supports such audits as part of its continuing effort to maintain high standards for human research protections. Entities that may audit IRBs may include but are not limited to: FDA, OHRP, , Joint Commission, ORO, and the accrediting organization under contract with VA. Sponsors or funding entities of research may also be authorized to audit specific documents and procedures.

1.1 Preparing for an Audit

For external audits involving OHRP or FDA, the following must be notified immediately:

- Institutional Official (Facility Director)
- ACOS/R&D
- AO/R&D
- IRB Chairperson(s)
- The Research Compliance Officers (RCOs)
- The Human Research Protection Program (HRPP) Coordinator
- The IRB staff designated to participate in the audit are required to follow the steps outlined by this institution for preparing the site for an audit.

1.2 Participating in an Audit

IRB staff is expected to know and follow the procedures outlined by this Institution for the conduct of a regulatory audit.

Prior to being granted access to IRB documentation, inspectors or auditors must exhibit proof of their authority or authorization to conduct the audit and to access IRB documents, and no entity other than those listed on the consent forms may have access to any document that includes subject identifiers.

Auditors will be provided with adequate working area to conduct an audit and IRB staff and members must make every reasonable effort to be available and to accommodate and expedite the requests of such auditors.

Documents may be copied and taken off-site only by individuals authorized by the Medical Center Director to do so.

1.3 Follow-up After an Audit

Reports of the audit, either verbal or written, should be addressed by the facility Director, Investigator and/or ACOS/R&D (with the assistance and support of the IRB Program Administrator, RCO, or HRPP Coordinator), as soon as possible after the audit.

Investigators should forward all external audit reports and action plans that address audit reports to the Research office when completed. The Research office will submit these audit results to ORO through the Institutional Official.

2. Scope

These policies and procedures apply to Investigators conducting human subjects' research in the Durham VAHCS.

3. Responsibility

Institutional Official is responsible for serving as the responsible institutional official in all regulatory agency matters regarding regulatory compliance, participating as needed in regulatory agency audits, and providing support in responding to and correcting audit findings.

ACOS/R&D is responsible for all formal regulatory agency correspondence and interactions, establishing logistical support during regulatory agency audits, serving as key institution contact during such audits, and drafting responses to regulatory agency correspondence received following such audits.

IRB Chairperson(s), Members and Staff, RCO, and HRPP Coordinator are responsible for participating in regulatory agency audits as determined by the ACOS/R&D, and to fully cooperate with government officials during participation in such audits.

IRB Chairperson, and the ACOS/R&D are responsible for assisting the IRB Program Administrator in formal responses to regulatory agency audits and in implementing policy and procedure changes indicated by such audits.

QA 903: STUDY SITE MONITORING VISITS

1. Policy

The Durham VAHCS acknowledges that certain regulatory agencies have the authority to monitor the procedures and specific documents of Investigator protocols, and supports such monitoring visits as part of its continuing effort to maintain high standards for human research protections. These monitoring visits may be routine or conducted for specific causes.

Entities that may monitor Investigators include but are not limited to: Contract Research Organizations (CROs), pharmaceutical companies otherwise known as sponsors, the Cooperative Studies Program, and other funding entities.

1.1 Preparing for a Monitoring Visit

Research staff responsible for scheduling site monitoring visits must notify the ACOS/R&D or designee immediately of scheduled visits using the CRA Monitoring Visit-Notification/Entrance form.

In addition, the Privacy Officer must also be notified and provided with a list of subjects that will be/may be monitored. The Privacy Officer must ensure that there is a signed HIPAA authorization for each subject whose research data will be monitored. Note: This means that prior to the monitoring visit, study monitors will need to provide Investigators with a list of subjects to be monitored so that the Investigator can in turn provide this list to the PO. If the monitor does not provide a list of subjects to be monitored, the PO may need to review all HIPAA authorizations for the study to ensure that study data may be reviewed.

VA will deny monitor access if a signed, valid HIPAA authorization cannot be produced.

If the monitoring visit is unscheduled, the ACOS/R&D (or designee) and Privacy Officer is to be notified as soon as the research staff is made aware of the visit.

1.2 Monitor Access to Pertinent Medical Records of VA Study Subjects

1.2.1 Limited Read-Only Access to Selected Data

A clinical patient group involving only study subjects who have consented to participate in the clinical trial and authorized the disclosure of their protected health information to clinical trial monitors consistent with the HIPAA Privacy Rule can be established within CPRS as an Order Entry/Results Reporting (OE/RR) list. Permissions can be set to allow only authorized individuals (including clinical trial monitors) to have read-only

access to these patient's records. For multi-site clinical trials involving a VA principal Investigator (e.g., VA, NIH, or industry sponsored study), read-only access of a clinical patient group can be provided through the Compensation and Pension Record Interchange (CAPRI) tool, which may allow better consistency in central monitoring. This process will be centrally managed through the Office of Health Information. Health Information Access (HIA) team (email: VHA 19 HDI HIA).

Under this option, monitors are required to complete the VA Information Security Awareness Training, VHA Privacy Policy Training, and sign the National Rules of Behavior. This training is available via the VA Talent Management System (TMS). The course generally takes one hour to complete and must be taken annually. This training is applicable to multiple studies reviewed by the same monitor.

In addition, monitors will have to provide their Social Security Number to asses CPRS. The VHA agrees not to use SSNs for any other purpose other than for the creation of the account. The user account should be set up to purge the SSNs from CPRS at the end of the session.

1.2.2 VA Employee Driver

A VA employee "driver" accesses the system with the monitor watching and shows the monitor only the information that the monitor needs and is authorized to see for the specific trial.

1.3 Participating in a Monitoring Visit

The Principal Investigator and his/her research staff are expected to know and follow the procedures outlined by this Institution and the Office of Research and Development for the conduct of a site-monitoring visit.

Contracts with sponsors or CROs must define the role of the study monitor as specified in this standard operating procedure.

Prior to being granted access to the Investigator's documentation, all monitors must sign in as a visitor at the Research Office using the CRA Monitoring Visit - Notification / Entrance form.

Monitors must exhibit proof of their authority or authorization to conduct the visit and to access Investigator documents. No entity other than those listed on the consent forms and/or HIPAA authorizations may have access to any document that includes subject identifiers.

The Principal Investigator or designee is to meet with the study monitor(s) prior to the monitors' beginning their work. The role of the monitor is to be reviewed during each

visit, including the VA requirement that any potential or actual serious findings be conveyed to the Investigator and the ACOS/R&D, Administrative Officer for Research (AO/R&D), or his/her designee (e.g., Research Compliance Officer) during an exit interview.

Monitors will be escorted through the medical center by the PI or his/her designee.

Monitors will be provided with an adequate working area to conduct their visit. The research staff must make every reasonable effort to be available and to accommodate and expedite the requests of the monitors.

1.4 Follow-up After a Monitoring Visit

Findings that require an exit interview include but are not limited to:

1) Any suspicions or concerns that serious non-compliance may exist, and
2) All findings of serious non-compliance with the study protocol, Institutional Review Board requirements, or applicable regulations and policies such as:
    a) Failure to consent subjects,
    b) Enrolling subjects who do not meet study inclusion criteria
    c) Failure to report serious unexpected and related adverse events.

Exit interviews must be scheduled by the Investigator, with the Monitor, ACOS/R&D, AO/R&D (or his/her designee) as soon as findings mentioned above are determined.

If the monitor records no serious findings or concerns as listed above, the Investigator or research coordinator must notify the research office in writing (using the CRA Monitoring Visit – Exit form) that there were no such findings identified by the monitor.

Investigators must forward all Monitoring Reports and action plans secondary to serious findings and/or concerns to the IRB as soon as possible after the monitoring visit. The Research Office is required to report to the Office of Research Oversight through the Medical Center Director all findings of serious noncompliance.

Reports of serious noncompliance will also be submitted immediately to the IRB Chairperson, to the IRB at the next convened meeting, and the Research & Development Committee.

Investigators must submit all monitoring reports to the IRB at the time of continuing review.

2. Scope

These policies and procedures apply to all Investigators conducting research at the Durham VAHCS.

3. Responsibility

Medical Center Director is responsible for serving as the responsible institutional official in all regulatory agency matters regarding regulatory compliance, participating as needed in regulatory agency audits, and providing support in responding to and correcting audit findings.

ACOS/R&D (or designee) is responsible for all formal regulatory agency correspondence and interactions, serving as key institution contact during audits, and drafting responses to regulatory agency correspondence received following such audits.

The Investigator is responsible for informing appropriate institutional officials of impending monitoring visits, scheduling entrance and exit briefings, and responding to all serious findings and/or concerns through the appropriate institutional and regulatory officials.

IRB Chairperson is responsible for assisting in implementing policy and procedure changes indicated by such audits.

QA 905: HUMAN SUBJECT RESEACH AUDITING PROGRAM

1. Policy

Research Compliance Officers and the Auditing of VHA Human Subjects Research to Determine Compliance with Applicable Laws, Regulations and Policies; the Durham VA HCSResearch Compliance Officer (RCO) will conduct Triennial Regulatory Audits and Annual Informed Consent Audits to assure compliance with Good Clinical Practice (GCP) Guidelines, as well as VHA Human Research Protection Program (HRPP) requirements. The RCO auditing program is a mechanism to evaluate safeguards in place at the Durham VAHCS to protect human research subjects in VA research, as well the HRPP.

1.1 Audit Program

Details of the human subject auditing program can be found in MCM 558-14-00.24, Research Compliance Program.

The facility Director is responsible for ensuring appropriate auditing of local human subjects research studies to assess compliance with all applicable local, VA, and other Federal requirements including, but not limited to, ORO requirements.

The facility Director is responsible for appointing an RCO to conduct annual research consent document audits, triennial regulatory audits (as required by the annual ORO requirements for Audits) and to assist in the facility assessment of regulatory compliance. The RCO reports directly to the facility Director. The Director must also report any appointment, resignation, or change in RCO status to ORO VHA Central Office within 5 business days after the RCO status change.

1.2 IRB Review of Audit Reports

The IRB will review all audit reports (either by the Chairperson or full committee review) and will determine any needed improvements and/or make recommendations to Investigators as a result of the audit (s). If the IRB determines that corrective actions are warranted, the IRB will inform the Investigator of the changes that need to be made and the timeframe in which changes should be made. If no changes or recommendations are made as a result of the audit, the IRB will acknowledge the report and will provide the Investigator with notification that the audit report was reviewed and acknowledged (see also SOP RR 403).

2. Scope

MCM 558-14-00.24 applies to all IRB and R&DC approved research being conducted at the Durham VAHCS.

3. Responsibilities

The Medical Center Director is responsible for the overall assurance of protections for human research participants within the Durham VAHCS.

The ACOS/R&D is delegated the responsibility for the implementation, conceptual oversight, and administrative leadership with regard to ensuring compliance and quality improvement for the HRPP.

The RCO is responsible for monitoring the HRPP by conducting audits as described in MCM 558-14-00.24.