Human Research Protection Program (HRPP) Policies and Procedures Manual

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ACRONYMS AND ABBREVIATIONS

AE	Adverse Event
ASL	American Sign Language
CFR	Code of Federal Regulations
CITI	Collaborative Institutional Training Initiative
CoC	Certificate of Confidentiality
COI	Conflict of Interest
DMC	Data Monitoring Committee
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DSMC	Data Safety Monitoring Committee
EC	Executive Committee
EHS	Environment, Health and Safety
FDA	Food and Drug Administration
FWA	Federal-wide Assurance
GC	General Counsel
GCP	Good Clinical Practices
HDE	Humanitarian Device Exemption
HUD	Humanitarian Use Device
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HRPP	Human Research Protection Program
HSR	Human Subjects Research
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IND	Investigational New Drug
IO	Institutional Official
IRB	Institutional Review Board
IT	Information Technology
IVD	In Vitro Device Product
LAR	Legally Authorized Representative
LDS	Limited Data Set
MCL	Michigan Compiled Law
MTA	Material Transfer Agreement
NHS	Non-Human Subjects (research)
NIH	National Institutes of Health
NSR	Non Significant Risk
OHRP	Office for Human Research Protections
OSR	Office of Sponsored Research/Grants and Contracts
PI	Principal Investigator
PHI	Protected Health Information
PHS	Public Health Service
PII	Personally Identifiable Information

PRIM&R	Public Responsibility in Medicine and Research
QA	Quality Assurance
QI	Quality Improvement
RCR	Responsible Conduct of Research
SR	Significant Risk
UAPs	Unanticipated Problems (Involving Risk to Subject or Others)
UADE	Unanticipated Adverse Device Effect
VAEI	Van Andel Education Institute
VAI	Van Andel Institute
VAIGS	Van Andel Institute Graduate School
VARI	Van Andel Research Institute

1 Human Research Protection Program

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

The VARI Human Research Protection Program (VARI HRPP) operates under the authority of the VARI policy "Human Research Protection Program (HRPP)" adopted on September 27, 2013. As stated in that policy, the operating procedures in this document "…serve as the governing procedures for the conduct and review of all human research conducted under the auspices of the VARI." These operating procedures are reviewed at least of annually by the HRPP Director, updated as warranted, and are made available to the VARI research community on the VARI Intranet HRPP site. Changes to these policies and procedures are communicated to the VARI research community by way of email notifications and are updated and highlighted on the VARI Intranet HRPP site (sp.vai.org/IRB).

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

1.1 Mission

The mission of the HRPP is to:

- Safeguard and promote the health and welfare of human research subjects by ensuring that their rights, safety and well-being are protected;
- Provide guidance and support to the research community in the conduct of research with human subjects;
- Assist the research community in ensuring compliance with relevant regulations;
- To provide timely and high quality education, review and monitoring of human research projects; and
- To facilitate excellence in human subjects research.
- The HRPP includes mechanisms to:
  - Monitor, evaluate and continually improve the protection of human research subjects.
  - Dedicate resources sufficient to do so.
  - Exercise oversight of research protection.
  - Educate PIs and research staff about their ethical responsibility to protect research subjects.
  - When appropriate, intervene in research and respond directly to concerns of research subjects.

1.2 Definitions

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

Human Subjects Research. – means any activity that meets the definition of "research" and involves "human subjects" as defined by either the Common Rule or FDA regulations. At VARI this also includes use of specimens with keys or codes to identifiers that may be held by an external investigator.

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

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

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

The Food and Drug Administration (FDA) has defined "research" as being synonymous with the term "clinical investigation". A clinical investigation, as defined by FDA regulations, means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the FDA under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [21 CFR 50.3(c), 21 CFR 56.102(c)]

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

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

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

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

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

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

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

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

a) **Human drugs** – The primary intended use of the product is achieved through chemical action or by being metabolized by the body. A drug is defined as a substance recognized by an official pharmacopoeia or formulary; a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; a substance (other than food) intended to affect the structure or any function of the body; a substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.) *http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm*

b) **Medical Devices** – A device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes." *http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm*

c) **Biological Products** – include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics

are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available. *http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm*

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

e) **Color Additives** – A color additive is any dye, pigment or substance which when added or applied to a food, drug or cosmetic, or to the human body, is capable (alone or through reactions with other substances) of imparting color. Color additives for use in food, drugs, and cosmetics require premarket approval. Color additives for use in or on a medical device are subject to premarket approval, if the color additive comes in direct contact with the body for a significant period of time. *http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm*

f) **Foods** – Foods include dietary supplements that bear a nutrient content claim or a health claim.

g) **Infant Formulas** – Infant formulas are liquid foods intended for infants which substitute for mother's milk.

h) **Electronic Products** – The FDA regulates certain classes of electronic products including radiation-emitting electronic products such as microwaves and x-rays.

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

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

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

Engagement. The following is based on the Office of Human Research Protection (OHRP) guidance on engagement in research. VARI is considered *engaged* in a research project when the involvement of their employees or agents in that project includes any of the following:

- Intervention for research purposes with any human subjects of the research by performing invasive or noninvasive procedures.
- Intervention for research purposes with any human subject of the research by manipulating the environment.

- Interaction for research purposes with any human subject of the research.
- Obtaining the informed consent of human subjects for the research.
- Obtaining for research purposes identifiable private information or identifiable biological specimens from any source for the research. In general, obtaining identifiable private information or identifiable specimens includes, but is not limited to:
  - Observing or recording private behavior,
  - Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens provided by another institution, and
  - Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the PIs.

1.3 Regulatory Compliance

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

Research supported by the **Department of Defense (DoD)** is reviewed and conducted in compliance with 32 CFR 219, 10 USC 980, applicable parts of title 21 CFR (50, 56, 312, 600, 812), DoD Instruction 3216.02, DoD Directive 3210.07, and applicable additional requirements from respective DoD component(s). Researchers should consult the applicable regulations, instructions, and directives when designing their research. These rules include but are not limited to:

- Special education requirements for Navy-funded funded human subjects research;
- Appointment of research monitor for all research involving more than minimal risk to research participants;
- Special protections for U.S. military personnel participating in research
- Disclosure and consent; and
- Prohibition of research involving Prisoners of War.

Review by the applicable DoD Human Research Protection Office (HRPO) and IRB may be required. VARI will execute a DoD FWA or DoD Addendum to its FWA when required by the involved DoD branch. The IRB will evaluate the research in accordance with these rules when applicable.

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

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

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

VARI voluntarily applies the International Conference on Harmonization (“ICH”) Good Clinical Practices (“GCP”) Guidelines (sometimes referred to as “ICH-GCP” or “E6”) to certain types of human subjects research conducted under its IRB. In general, VARI applies the ICH-GCP guidelines only to the extent that they are compatible with FDA and DHHS regulations.

1.4 Federalwide Assurance (FWA)

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

VARI has an OHRP-approved Federalwide Assurance FWA00004131 and has designated one IRB (registered as IORG0002610) to review all human research protocols.

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

1.5 VARI HRPP Structure

The HRPP is a comprehensive system to ensure the protection of human subjects participating in research. It consists of various individuals and committees such as: the Institutional Official, the HRPP Director, the IRB Specialist and staff, the IRB, other committees or subcommittees addressing human subjects protection (e.g., the Institutional Biosafety Committee, Radiation Safety Committee, Conflict of Interest Committees), PIs, research staff, health and safety staff (e.g., Biosafety Officer, Radiation Safety Officer, Environment, Health and Safety Manager). The objective of this system is to assist the institution in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

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

1.5.1 Institutional Official

The ultimate responsibility of the HRPP resides with the **Institutional Official (IO)** of the program. The IO is legally authorized to represent VARI. He/she is the signatory of the FWA and assumes the obligations of the FWA. The IO is responsible for ensuring that the VARI HRPP and IRB has the resources and support necessary to comply with all institutional policies, laws, and regulations that govern human subjects research. Such resources include, but are not limited to:

- Staffing commensurate with the size and complexity of the research program;
- Appropriate office space, equipment, materials, and technology;
- Resources for the production, maintenance, and secure storage of HRPP and IRB records;
- Resources for auditing and other compliance activities and investigation of non-compliance;
- Access to general counsel; and
- Supporting educational opportunities related to human research protections for IRB members, relevant administrative staff, and all members of the research team.
- The IO conducts and documents an annual review of HRPP and IRB function, requirements, and resources and makes adjustments as needed.

- The IO is also responsible for:
  - Fostering, supporting and maintaining an institutional culture that supports the ethical conduct of all research involving human subjects and the adherence to regulations and institutional policies;
  - Ensuring that the IRB functions independently by, among other mechanisms, being directly accessible to the IRB Chair(s) and members if they experience undue influence or if they have concerns about the function of the IRB;
  - Oversight of the Institutional Review Board (IRB);
  - Oversight over the conduct of research conducted by all VARI PIs;
  - Assuring the IRB members are appropriately knowledgeable to review research in accordance with ethical standards and applicable regulations;
  - Assuring that all PIs are appropriately knowledgeable to conduct research in accordance with ethical standards and applicable regulations; and
  - Oversight of the development and implementation of an educational plan for IRB members, staff and PIs.

The IO must complete the OHRP Human Subject Assurance Training (available at: http://www.hhs.gov/ohrp/education/training/introduction.html) and any other appropriate training on human research protections, including CITI. The HRPP Office will provide on-going continuing education for the IO concerning human research protections. The IRB Executive Committee meets with the IO periodically to discuss current issues and provide updates at least semi-annually. In addition, the IO is invited to attend IRB inservices that are provided by external consultants, webinars, as well as presentations by IRB members.

The designated IO is made known to employees of the organization and is accessible by phone, email, in person or other methods of communication. The IRB Chair and HRPP Director have access to the IO for any concerns or issues related to the HRPP.

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

1.5.2 HRPP Director

The HRPP Director is selected by and reports to the IO and is responsible for:

- Developing, managing and evaluating policies and procedures that ensure compliance with all state, and federal regulations governing research. This includes monitoring changes in regulations and policies that relate to human research protection and overseeing the administration of the IRB.
- Advising the IO on key matters regarding research at VARI.
- Implementing the institution's HRPP policies and procedures.
- Submitting, implementing and maintaining an approved FWA through the IO and the Department of Health and Human Services Office of Human Research Protection (OHRP).

- Managing the finances of VARI IRB.
- Assisting PIs in their efforts to carry out VARI's research mission.
- Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program.
- Developing training requirements as required and as appropriate for PIs, subcommittee members and research staff, and ensuring that training is completed on a timely basis.
- Serving as the primary contact at VARI for the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services, the Food & Drug Administration (FDA) and other federal regulatory agencies.
- Day-to-day responsibility for the operation of the HRPP office, including supervision of HRPP and IRB staff.
- Responding to questions regarding the protection of human subjects.
- Working closely with the Chair of the IRB on the development of policy and procedures, as well as organizing and documenting the review process.

1.5.3 HRPP Staff

In addition to the leadership structure described above, other support staff members for the HRPP and IRB include the Compliance Specialist and Compliance Department Administrative Assistant. The HRPP and IRB staff for VARI must comply with all ethical standards and practices. The duties and responsibilities for all staff are found in their respective job descriptions, and their performance is evaluated on an annual basis. The VARI HRPP and IRB Office reports to the HRPP Director, who has day-to-day responsibilities for its operations.

1.5.4 Institutional Review Board (IRB)

VARI has one IRB, appointed by the IO. The IRB prospectively reviews and makes decisions concerning all human research conducted at VARI facilities, by its employees or agents, or under its auspices unless another IRB has been designated to do so. Only HRPP accredited IRBs can be designated as another IRB of record. The IRB is responsible for the protection of rights and welfare of human research subjects at the VARI. It discharges this duty by complying with the requirements of federal and state regulations, the FWA, and institutional policies. (See Section 2 for a detailed discussion of the IRB.)

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

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

1.5.5 General Counsel's Office

The VARI HRPP relies on the General Counsel for the interpretations and applications of Michigan state law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research.

1.5.6 Department Chairs and Institutional Leaders

Department Chairs and institutional leaders are responsible for ensuring that the Principal Investigator (PI) is qualified by training and experience to conduct the proposed research. For each protocol submitted to VARI IRB for review, the department chair must certify that s/he accepts responsibility for assuring adherence to the federal and state regulations and VARI policies governing the protection of human subjects of research, including applicable VARI credentialing requirements.

Department chairs are responsible for assuring that PIs have the resources required to conduct the research in a way that will protect the right and welfare of subjects. Such resources include but are not necessarily limited to personnel, space, equipment and time.

Department chairs are required to review all proposals before they are submitted to the IRB for review. The signature of the Department chair indicates that (1) the PI is qualified and has the necessary resources to safely conduct the study, and (2) that the study is found to be scientifically sound and can reasonably be expected to answer the proposed research question.

1.5.7 The Principal Investigator (PI)

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

For more information on Investigator Responsibilities, see *Section 15.*

1.5.8 Other Related Units

1.5.8.1 Office of Grants and Contracts

The Office of Sponsored Research/Grants and Contracts (OSR) staff review all research agreements with federal, foundation, or non-profit sponsors. This review ensures that all terms of the award are in compliance with VARI policies. Only designated senior individuals within the OSR have the authority to approve research proposals and to execute research agreements on behalf of VAI.

When the grant or contract agreement includes human research activities that will be conducted by PIs who are not employees or agents of VARI, a subcontract is executed between VARI and the collaborating institution. The subcontract includes the requirement for the collaborating institution to

assure compliance with federal regulations for the protection of human subjects in research and to provide documentation of current and ongoing IRB approval by submission of an executed Form 310 (as applicable). The collaborating institution must also ensure that key personnel involved in human subjects research are in compliance with the NIH policy on education in the protection of human research subjects and provide documentation of education of key personnel to VARI.

1.5.8.2 Business Development/Tech Transfer (protecting proprietary information)

The Business Development Department supports all research involving industry or external funds, including forging new relationships/collaborations, review and preparation of legal agreements, etc.

The Business Development (BD) Department assists PIs in the process of identifying funding from for-profit entities and works with the Office of Sponsored Research/Grants and Contracts (OSR) in procuring research funding from industry sources. BD staff facilitates this by developing new relationships and building partnerships with potential for-profit collaborators that foster scientific exchange, as well as preparation and review of legal agreements, etc. During the preparation and review of industry-based research agreements, the OSR staff is charged with confirmation that the appropriate IRB and IACUC protocol internal grant comparison approvals are in place for any proposed research performed by VARI PIs prior to the commencement of work on the project.

Oversight of externally sponsored research activities is accomplished through the efforts of the OSR. The OSR supports PIs with applications for, and administration of, extramurally funded research projects. OSR provides oversight in the application and funding process, and assist PIs in fulfilling their scheduled deliverables, reporting, and overall programmatic compliance requirements to funding agencies.

Technology transfer refers to the activities of professional staff to develop and commercialize marketable technologies for the public good. Technology is typically transferred through an agreement in which VARI grants a license to a third party. The license allows the third party to use VARI's intellectual property rights in the defined technology, sometimes for a particular field of use and/or region of the world. Licenses include terms that require the licensee to meet development milestones and to make financial payments to VARI. These payments are shared with the inventors, labs, and re-invested in VARI's budget to provide support for further research, education and participation in the technology transfer process.

1.5.8.3 Environment, Health and Safety

The Environment Health and Safety (EHS) Office provides guidance and education to promote health, safety, protection of the environment, and assure regulatory compliance.

Research involving biological, chemical, or radioactive materials require additional approval from VARI committees/boards, in accordance with related VARI policies, including:

- VAI Radiation Safety Manual
- VARI Chemical Hygiene Plan
- VARI Bloodborne Pathogens Exposure Control Plan

1.5.9 Protocol-specific coordination

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

- Permission to enter classrooms or hospital units
- Permission from external research locations, including associated IRB(s), if required (e.g., Spectrum Hospital, Saint Mary's/Mercy Health, Hudsonville School District)
- Departmental approvals
- Institutional Biosafety Committee
- Radiation Safety Committee
- Safety Committee
- Conflict of Interest Committee

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

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

1.6 Collaborative Research Projects

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

It is the policy of VARI to assure that all facilities participating in a human subjects study receive adequate documentation about the study in order to protect the interests of study subjects. Before a study can begin, it must be approved by the IRBs of record for each participating facility and, where appropriate, the IRB of record for the coordinating facility.

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

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

When following Department of Defense regulations, when VARI conducts multi-site research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.

If VARI is the coordinating facility, the PI must document how the conduct of the protocol and the protection of human subjects will be communicated to and among the other participating facilities engaged in the research study. The PI is responsible for serving as the liaison with regulatory and funding agencies, with other participating facilities, and for all aspects of internal review and oversight procedures. The PI is responsible for ensuring that all participating facilities obtain review and approval from their IRB of record and adopt all protocol modifications in a timely fashion. The PI is responsible for ensuring that the research study is reviewed and approved by any other appropriate committees at the coordinating facility and at the participating facilities prior to enrollment of subjects.

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

- During the initial IRB submission of the multi-site study, the PI indicates in writing on the application form or in an application letter that VARI is the coordinating facility of a multi-site study.
- The PI submits the following information in their IRB application materials:
  - Whether research activities at participating institutions are defined as engagement;
  - Name of each participating facility;
  - Confirmation that each participating facility has an FWA (including FWA number);
  - Contact name and information for PI at each participating facility;
  - Contact name and information for IRB of record at each participating facility;
  - Method for assuring all participating facilities have the most current version of the protocol;
  - Method for confirming that all amendments and modifications in the protocol have been communicated to participating sites;
  - Method for communicating to participating facilities any serious adverse events and unanticipated problems involving risks to subjects or others; and
  - Method of communicating regularly with participating sites about study events.
- The PI submits approval letters from all of the IRBs of record for all participating sites.
- The PI maintains documentation of all correspondence between participating sites and their IRBs of record.

When VARI is engaged in research in part or in full, the VARI IRB will review the project.

2 Institutional Review Board

The Van Andel Research Institute (VARI) has established an Institutional Review Board (IRB) to ensure the protection of human subjects in human subjects research conducted under the auspices of the Organization. All non-exempt human subjects research conducted under the auspices of VARI must be reviewed and approved by VARI IRB or another institutionally designated IRB prior to the initiation of the research.

2.1 IRB Authority

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

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

The IRB functions independently. Attempts to coerce or otherwise unduly influence the actions of the IRB are forbidden by policy. Likewise, the IRB must remain free from the influence of financial and other organizational interests.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the institution. However, those officials may NOT approve research if it has not been approved or has been disapproved by the IRB. VARI officials may strengthen requirements and/or conditions, or add other modifications to secure VARI approval or approval by another VARI committee. Previously approved research proposals and/or consent forms must be re-approved by the IRB before initiating the changes or modifications.

2.2 Roles and Responsibilities

2.2.1 Chair of the IRB

VARI IO, in consultation with the HRPP Director, appoints a Chair and Vice Chair of the IRB to serve for renewable three-year terms. Any change in appointment, including reappointment or removal, requires written notification.

The IRB Chair should be a highly respected individual, from within VARI, fully capable of managing the IRB, and the matters brought before it with fairness and impartiality. The task of making the IRB a respected part of the VARI community will fall primarily on the shoulders of the Chair. The IRB must be perceived to be fair, impartial and immune to pressure by VARI's administration, the PIs whose protocols are brought before it, and other professional and nonprofessional sources.

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

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

The IRB Chair advises the IO and the HRPP Director about IRB member performance and competence.

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

2.2.2 Vice Chair of the IRB

When the IRB Chair is absent or is required to be recused, i.e. the Chair has a conflict of interest, the Vice Chair, or designee, will serve as the Acting Chair. The Vice Chair, or designee, has the same authority and duties as the Chair.

2.2.3 IRB Executive Committee (EC)

The IRB EC constitutes the senior leadership of the IRB with responsibility to review issues and make recommendations to the full IRB for their consideration and vote. The IRB EC is led by the IRB Chair and its members include the IRB Vice Chair, HRPP Director and IRB Specialist. The IRB EC facilitates IRB review and decision-making but does not have decision-making responsibility itself. Matters that will be considered by the IRB EC include policies related to new mandates from OHRP, the FDA, the NIH, the NCI, etc. The IRB EC will also review matters of major concern, such as reports of suspected non-compliance, deviations from approved protocols, major safety issues, and other matters related to human subjects research which require fact finding to facilitate review and decision making by the full IRB. The IRB EC meets on an ad hoc basis, when determined necessary at the request of the IRB members, the IRB Chair or any member of the IRB EC. (The IRB EC Charter can be found on the IRB SharePoint site.)

2.2.4 Subcommittees of the IRB

The IRB Chair, in consultation with the HRPP Director, may designate one or more IRB members to a subcommittee of the IRB to perform duties, as appropriate, to review and undertake other IRB functions, and to make recommendations to the IRB. The IRB Chair, in consultation with the HRPP Director, will appoint IRB members to serve on each IRB subcommittee created under this Section. The number and composition of the IRB subcommittee members shall depend on the authority delegated by the IRB Chair to such IRB subcommittee (e.g., merely making recommendations versus decision-making authority).

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

2.3 IRB Membership

IRB members are selected based on appropriate diversity, including consideration of race, gender, cultural backgrounds, specific community concerns in addition to representation by multiple, diverse professions, knowledge and experience with vulnerable subjects, and inclusion of both scientific and non-scientific members. The structure and composition of the IRB must be appropriate to the amount and nature of the research that is reviewed. Every effort is made to have member representation that has an understanding of the areas of specialty that encompasses most of the research performed at VARI. VARI has procedures (See *Section 3*) that specifically outline the requirements of protocol review by individuals with appropriate scientific or scholarly expertise.

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

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

Individuals from VARI's Offices of Sponsored Research/Grants and Contracts, Business Development or Technology Transfer may not serve as members of the IRB or carry out day-to-day operations of the review process. Individuals from these offices may provide information to the IRB and attend IRB meetings as invited guests.

2.4 Composition of the IRB

The IRB will have at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.

The IRB will be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

In addition to possessing the professional competence necessary to review specific research activities, the IRB will be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.

The IRB will therefore include persons knowledgeable in the following areas:

- If the IRB regularly reviews research that involves a vulnerable category of subjects (e.g., children, prisoners, pregnant women, or handicapped or mentally disabled persons), consideration will be given to the inclusion of one or more individuals on the IRB, who are knowledgeable about and experienced in working with these subjects.
- Every nondiscriminatory effort will be made to ensure that the IRB does not consist entirely of men or entirely of women, including VARI"s consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. The IRB shall not consist entirely of members of one profession.

- The IRB includes at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.
- The IRB includes at least one member who is not otherwise affiliated with VARI and who is not part of the immediate family of a person who is affiliated with VARI.
- The IRB includes at least one member who represents the general perspective of participants.
- One member may satisfy more than one membership category.
- The IRB Chair and Vice-Chair are voting members of the IRB.
- Staff of VARI'S IRB Office may be voting members of the IRB.

On an annual basis, the IRB Chair, IRB Vice Chair and the HRPP Director shall review the membership and composition of the IRB to determine if they continue to meet regulatory and institutional requirements. Changes in IRB membership will be reported to the OHRP within 90 days of the change.

2.5 Appointment of Members to the IRB

The IRB Chair, Vice Chair and/or the HRPP Director, identifies a need for a new, replacement, or alternate member. The IRB nominates candidates and sends the names of the nominees to the IRB Office. Department Chairs and others may forward nominations to the IO, or to the IRB Office, or to an IRB Chair.

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

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

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

2.6 Alternate members

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

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

2.7 IRB Member Conflict of Interest

No IRB member or alternate may participate in the review (initial, continuing, or modification) of any research project in which the member has a conflict of interest (COI), except to provide information as

requested. It is the responsibility of each IRB member to disclose any COI in a study submitted for review and recuse him/herself, by leaving the room, prior to the final deliberations and vote.

All members and alternate members of the IRB complete a VARI Conflict of Interest Disclosure Form when first appointed and annually thereafter. If a member responds affirmatively to the existence of a potential conflict, the Compliance Director is notified. Potential COIs of IRB members are reviewed by the COI Committee to determine if an actual conflict exists. A listing of COI's of IRB members and/or alternate members are provided to the HRPP Director, IRB Chair and Vice Chair. At VARI, the HRPP Director and Compliance Director is the same person. The HRPP Director, IRB Chair and Vice Chair use this listing to ensure that IRB members and alternates are not assigned to conduct reviews of studies for which they have a conflict and to ensure appropriate recusal during convened meetings.

An IRB member, alternate, or consultant may be considered to have a conflicting interest requiring recusal when they, or an immediate member of their family, have any of the following:

- Substantive involvement in the design, conduct, and reporting of the research.
- Significant financial interests (See *COM-POL-001.01 Financial Conflict of Interest Policy* for a definition of significant financial interests) related to the research being reviewed.
- Any other situation where an IRB member or alternate member believes that another interest conflicts with his or her ability to deliberate objectively on a protocol.

The IRB Chair will poll IRB members at each convened meeting to determine if a COI exists regarding any protocol to be considered during the meeting and reminds them that they should recuse themselves by leaving the room during the discussion and vote of the specific protocol. If a conflicted member is participating by conference call, videoconference or web meeting the member's participation is terminated for discussion and voting.

IRB members with a conflicting interest are excluded from being counted towards quorum. All recusals by members with COI are recorded in the minutes.

If the COI status of an IRB member changes during the course of a study, the IRB member is required to declare this to the IRB Chair and/or HRPP Director.

2.8 Use of Consultants

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

Key information provided by consultants at meetings will be documented in the minutes. Written reviews and/or written statements provided by the consultants will be filed with the IRB protocol file.

The HRPP Director reviews the VAI COI policies (COM-POL-001.01 Financial Conflict of Interest Policy, COM-POL-002.01 Conflict of Commitments Policy, COM-POL-009 Institutional Conflict of Interest Policy) with consultants to the IRB. Consultants must verbally confirm to the HRPP Director that they do not have a COI prior to reviewing the project. Individuals who have a conflicting interest or whose spouse or immediate family members have a COI in the sponsor of the research cannot provide consultation.

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

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

2.9 Duties of IRB Members

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

IRB members reviewing research under expedited review should respond within one week of receipt.

2.10 Attendance Requirements

Members should attend at minimum seven of twelve meetings that are scheduled per year (refer to Section 3.5.1). If a member is unable to attend a scheduled meeting, they should inform the IRB Chair, Vice Chair, or IRB Office staff. If the inability to attend will be prolonged, a request for an alternate to be assigned may be submitted to the IRB Chair or the HRPP Director.

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

2.11 Training/Ongoing Education of the HRPP Director, and IRB Chair, Members, and Staff

A vital component of a comprehensive human research protection program is an education program for the HRPP Director, IRB Chair, Vice Chair and members. VARI is committed to providing training and an on-going educational process for IRB members and the staff of the HRPP Office, related to ethical concerns and regulatory and institutional requirements for the protection of human subjects.

2.11.1 Orientation

New IRB members, including alternate members will meet with the IRB Chair, Compliance Specialist or HRPP Director for an informal orientation session. At the session, the new member will be given a copy of the text, *Institutional Review Board—Management and Function* that includes the:

- Belmont Report,
- Federal regulations relevant to the IRB,

- Web address of the VARI Policies and Procedures for the Protection of Human Subjects.

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

2.11.2 Initial Education

The HRPP Director, IRB Chair, Vice Chair, Members, and Staff are required to complete the following courses in the CITI online Training Program or request the HRPP Director consideration of applicable training that can be substituted for the training listed below:

- Human Subjects Research Training – IRB Chair and Vice Chair Course (IRB Chair and Vice Chair only)
- Human Subjects Research Training – IRB Member Basic Course
- Good Clinical Practice (GCP) Training – IRB Members Basic Course
- Responsible Conduct of Research (RCR) – IRB Members Basic Course
- Conflict of Interest Course

2.11.3 Continuing Education

To ensure that oversight of human research is ethically grounded and the decisions made by the IRB is consistent with current regulatory and VARI policy requirements, training is continuous for IRB members throughout their service on the IRB. (See *Guidelines for VARI HRPP Training Requirements* for additional information.)

In addition to initial training requirements, the HRPP Director, IRB Chair, Vice Chair, Members, and Staff must also satisfy continuing education requirements on an annual basis. VARI uses the following activities as a means for offering continuing education to IRB members, HRPP Director, and IRB staff:

- In-service training at IRB meetings that include current hot topics;
- Local and regional training workshops and conferences;
- *Institutional Review Board—Management and Function*, Bankert & Amdur, eds.
- *IRB Ethics and Human Research*, bi-monthly publication of the Hastings Center
- Identification and dissemination by the HRPP Director or IRB Office staff of new information that might have affected the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues to IRB members via email, mail, or during IRB meetings.

The HRPP Director, IRB Chair, Vice Chair, Members, and Staff are also required to complete additional CITI training every 3 years, except for Conflict of Interest Training, as part of the VARI continuing education requirements.

- Human Subjects Research Training – IRB Chair and Vice Chair Course (IRB Chair and Vice Chair only)
- Human Subjects Research Training – IRB Member Refresher Course
- Good Clinical Practice (GCP) Training – IRB Members Basic Course

- Responsible Conduct of Research (RCR) – IRB Members Refresher Course
- Conflict of Interest Course (Every 4 years)

The activities for continuing education vary on a yearly basis depending on operating budget and areas of need, as determined by the HRPP Director. The HRPP Director and the IRB Chair determine which continuing education activities are mandatory for IRB members and staff in a given year and tracks whether each individual has satisfied the requirements. Initial and continuing education is tracked by the IRB Specialist through use of a spreadsheet that is updated on a monthly basis or more frequently as needed. Continuing non-compliance will result in the individual not being renewed as an IRB member. Completion of training requirements is included as part of the evaluation of the performance of HRPP staff.

The IO will provide support to send as many members of the IRB as possible to attend regional conferences and when possible, the annual PRIM&R conference on human research protections.

2.12 Liability Coverage for IRB Members

VARI's insurance coverage applies to employees and any other person authorized to act on behalf of VARI IRB or acts of omission within the scope of their employment for authorized activity.

2.13 Review of IRB Member Performance

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

2.14 Reporting and Investigation of Allegations of Undue Influence

If an IRB chair, member, or staff person feels that the IRB has been unduly influenced by any party, they shall make a confidential report to the HRPP Director or IO, depending on the circumstances. The IO will ensure that a thorough investigation is conducted. If the allegation is determined valid, a corrective action is put in place by the IO or delegated authority to prevent additional occurrences.

3 IRB Review Process

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

- Exempt
- Expedited Review
- Full Committee Review

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

VARI currently has Reliance Agreements with Michigan State University (MSU) and Spectrum Health to provide IRB oversight for defined studies. The IO, at his/her discretion, may choose to enter into an agreement, to cede review to another external IRB for a specific study or groups of studies. However, this is uncommon, unless required as a condition of an award or agreement. VARI will only rely upon another IRB when that IRB is part of an HRPP accredited program.

All IRB applications, forms, templates, and checklists are available at sp.vai.org/IRB.

3.1 Definitions

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

Minor Change. A minor change is one which makes no substantial alteration in:

- The level of risks to subjects,
- The research design or methodology (adding procedures that are not eligible for expedited review (See *Section 3.4*) would not be considered a minor change),
- For studies that are no more than minimal risk, the number of subjects enrolled in the research (no greater than 10% of the total requested),
- The qualifications of the research team,
- The facilities available to support safe conduct of the research,
- Any other factor which would warrant review of the proposed changes by the convened IRB.

For Studies currently closed to accrual, all study procedures completed, now in long-term follow-up would also be considered a minor change or minor alteration in a currently approved protocol.

Quorum. A quorum of the IRB consists of a simple majority of the voting membership, including at least one member whose primary concern is in a non-scientific area. If research involving an FDA-regulated article is involved, a licensed physician must be included in the quorum.

Suspension of IRB approval. A suspension is a directive of the convened IRB or other authorized individual (See *Section 5*) to temporarily stop some or all previously approved research activities. Suspended protocols remain open and require continuing review.

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

3.2 Human Subjects Research Determination

PIs are required to complete the *Non-Human Subjects Research Application (HRPP-FORM-002)* for activities they believe constitute non-human subjects research. The *Non-Human Subjects Research Application* solicits pertinent information in order to make the non-human subjects determination.

Determinations as to whether an activity constitutes human subjects research will be made according to the definitions in *Section 1.2*. Determinations regarding activities that are either clearly or clearly not human subjects research, may be made by the HRPP Director or the IRB Compliance Specialist. Determinations regarding less clear-cut activities will be referred to the IRB Chair, who may make the determination or refer the matter to the full IRB.

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

3.3 Exempt Studies

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

The designee may be a voting member of the IRB, an IRB Compliance Specialist or HRPP Director. Individuals involved in making the determination of IRB exempt status of a proposed research project cannot be involved in the proposed research. Reviewers cannot have any apparent conflict of interest. Identification of individuals designated to conduct exempt determinations will be made in writing. Voting members who are designated to conduct exempt determinations will be noted on the IRB roster, which is maintained in the IRB office.

Studies that are determined to be exempt from the Common Rule (45 CFR 46), are not exempt from VARI review and approval. Although exempt research is not covered by the federal regulations, this research is not exempt from ethical considerations, such as the principles described in the Belmont Report. The individual making the determination of exemption will determine whether to require additional protections for subjects in keeping with ethical principles.

3.3.1 Limitations on Exemptions

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

Prisoners: Exemptions DO NOT apply to prisoners and IRB review is required**.**

3.3.2 Categories of Exempt Research

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

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:
   a. Research on regular and special education instructional strategies, or
   b. Research on the effectiveness of, or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
   a. Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects, and
   b. Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation.
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (2), if:
   a. The human subjects are elected or appointed public officials or candidates for public office, or
   b. Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the PI in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

   NOTE: In order to be eligible for this exemption, all of the materials have to exist at the time the research is proposed.
5. Research and demonstration projects which are conducted by or subject to the approval of federal department or agency heads, and which are designed to study, evaluate, or otherwise examine:
   a. Public benefit or service programs,
   b. Procedures for obtaining benefits or services under those programs,
   c. Possible changes in or alternatives to those programs or procedures, or
   d. Possible changes in methods or levels of payment for benefits or services under those programs.
   e. The program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older American Act).

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

6. Taste and food quality evaluation and consumer acceptance studies,

   a. If wholesome foods without additives are consumed, or

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

3.3.3 FDA Exemptions

The following category of clinical investigations is exempt from the requirements of IRB review:

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

3.3.4 Procedures for Exemption Determination

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

- A completed *Exempt Research Application (HRPP-FORM-007)*,
- All recruitment materials (e.g., letter of invitation, recruitment script, flyer),
- Consent form (when appropriate),
- All surveys, questionnaires, instruments, etc.,
- Letter(s) of permission from each non-Organization site of performance,
- If sponsored, one copy of the grant application(s) and/or contract,
- Verification of current human research protection training for all members of the research team, including the faculty advisor.

The IRB Chair (or designee) reviews all requests for exemptions and determines whether the request meets the criteria for exempt research.

To document the reviewer's determination of the request for exempt research, he/she completes the *Exemption* Determination *Checklist (HRPP-CHK-006).* The reviewer verifies on the form whether the submission meets the definition of human subjects research (See *Section 1.2*). If the request meets the definition of human subject research, the reviewer then determines whether or not the research is eligible for exemption. Although exempt research is not covered by the federal regulations, this research is not exempt from the ethical guidelines of the Belmont Report. The individual making the determination of exemption will determine whether to require additional protections for subjects in

keeping with the guidelines of the Belmont Report. The reviewer indicates whether the request for exemption was approved or denied. If approved, the rationale for the determination and category under which it is permitted must be indicated. The exempt application, review, and determination letter are recorded and maintained in the same manner and for a minimum of seven years after completion of the study.

Once IRB review is completed, IRB staff will send the determination letter to the PI with the results of the review.

Exempt determinations will include a termination date, with the maximum time allotted being 3 years. If the research extends beyond the termination date, the researcher must submit a new application to request continuation of the study exemption. This process will allow the PI and the VARI the opportunity to review and update the research activity and determine whether the study still qualifies for exemption. PIs must notify the IRB office when an exempt research project is complete so that an accurate database of active research activities is maintained.

3.4 Expedited Review

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

- Some or all of the research appearing on the list of categories of research eligible for expedited review and found by the reviewer(s) to involve no more than minimal risk,
- Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

3.4.1 Categories of Research Eligible for Expedited Review

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

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

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

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

The expedited review procedure may not be used for classified research involving human subjects. The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened meeting--utilized by the IRB.

Research Categories one (1) through seven (7) pertain to both initial and continuing IRB review:

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
   a. Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
   b. Research on medical devices for which (i) an investigational device exemption application (21 CFR 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
   a. From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week, or
   b. From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week. [Children are defined in the DHHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.
3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples:
   a. Hair and nail clippings in a non-disfiguring manner;
   b. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
   c. Permanent teeth if routine patient care indicates a need for extraction;
   d. Excreta and external secretions (including sweat);
   e. Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue;
   f. Placenta removed at delivery;
   g. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
   h. Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
   i. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
   j. Sputum collected after saline mist nebulization.
   k. Vaginal swabs that do not go beyond the cervical os; rectal swabs that do not go beyond the rectum; and nasal swabs that do not go beyond the nares.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples:
    a. physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
    b. weighing or testing sensory acuity;
    c. magnetic resonance imaging;
    d. electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
    e. moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). [NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46 101(b)(4). This listing refers only to research that is not exempt.]
6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. [NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.]

    Categories 8 and 9 apply only to continuing review.

8. Continuing review of research previously approved by the convened IRB as follows:
    a. where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; *or*
    b. where no subjects have been enrolled and no additional risks have been identified; *or*
    c. where the remaining research activities are limited to data analysis.

    [Of note, category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed by a convened IRB may undergo subsequent continuing review by the expedited review procedure. For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8)(a), (b), or (c) are satisfied for that site. However, with respect to category 8(b), while the criterion that "no subjects have been enrolled" is interpreted to mean that no subjects have ever been enrolled at a particular

site, the criterion that "no additional risks have been identified" is interpreted to mean that neither the PI nor the IRB at a particular site has identified any additional risks from any site or other relevant source.]

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

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

3.4.2 Expedited Review Procedures

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

On an annual basis, the IRB Chair will designate a list of IRB members eligible to conduct expedited review. The designees must be experienced (having served on the IRB for at least one year, has served on the IRB for a minimum of 3 months and has been mentored by either the IRB Chair or HRPP Director and has attended an in-service workshop on expedited review criteria and are voting members or alternate members of the IRB. The IRB Staff will select expedited reviewers from that list. Selected reviewers will have the qualifications, experience and knowledge in the content of the protocol to be reviewed, as well as be knowledgeable of the requirements to approve research under expedited review. IRB members with a conflict of interest in the research (see *Section 2.7*) cannot be selected.

When reviewing research under an expedited review procedure, the IRB Chair, or designated IRB member(s), will receive and review all documents that would normally be submitted for a full-board review. This requirement applies to all categories of submissions including initial reviews, continuing reviews, and protocol modifications. The reviewer will determine and document the regulatory criteria allowing use of the expedited review procedure by using the *Expedited Review Determination Checklist (HRPP-CHK-005).*

If the research meets the criteria allowing review using the expedited procedure, the reviewer(s) conducting initial or continuing review complete the appropriate checklist *Initial Protocol Review Checklist (HRPP-CHK-004)* or *Continuing Review Checklist (HRPP-CHK-003)*.The checklist(s) will assist in determining whether the research meets the regulatory criteria for approval. The same criteria of approval apply to reviews conducted via expedited review as those conducted by the convened board. If the research does not meet the criteria for expedited review, then the reviewer will indicate that the research requires full review by the IRB and the protocol will be placed on the next IRB meeting agenda.

In reviewing the research, the reviewers will follow the Review Procedures described in *Sections 3.6* and *3.7* and may exercise all of the authorities of the IRB except that the reviewers may not disapprove

the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure by the convened IRB.

Reviewers will indicate approval, required modifications or requirement for convened IRB review on the *Initial Protocol Review Checklist (HRPP-CHK-004) or Continuing Review Checklist (HRPP-CHK-003)* and return it to the IRB Office. If modifications are required, the IRB Office staff will inform the PI in writing.

In the event that expedited review is carried out by more than one IRB member and the expedited reviewers disagree, the protocol will be submitted for review at the next convened IRB meeting.

3.4.3 Informing the IRB

Through a list appended to the agenda for the next scheduled meeting, IRB members will be apprised of all expedited review approvals. Information for each action reviewed by the expedited review process, there will also be a notation citing the expedited regulatory category(ies) that is/are met. Any IRB member can request review of the protocol at a fully convened meeting, by contacting the IRB Office.

3.5 Convened IRB Meetings

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

3.5.1 IRB Meeting Schedule

The IRB meets on a regular basis throughout the year (once per month, usually on the second or third Wednesday). The schedule for the IRB may vary due to holidays or lack of quorum. The schedule for IRB meetings can be found on the VARI intranet site (sp.vai.org/IRB) Special meetings may be called at any time by the IRB Chair or the Vice Chair in conjunction with the HRPP Director and/or IRB Compliance Specialist.

3.5.2 Preliminary Review

The IRB Compliance Specialist will perform a preliminary review of all protocol materials submitted to the IRB Office for determination of completeness and accuracy, including use of an *Informed Consent Checklist (HRPP-CHK-011).* Only complete submissions will be placed on the IRB agenda for review. The PI will be informed either by e-mail, phone or in person of missing materials or missing information and informed of the submission deadline for this additional information in order for the study to be included on that month's agenda. In the case of a PI who is submitting a protocol for the first time or a PI who may not be well-versed in the protocol submission procedures, consultations can be arranged with the IRB Compliance Specialist or individual IRB members to assist in this regard.

3.5.3 Primary Reviewer

After it has been determined that the protocol submission is complete, the IRB Compliance Specialist will assign protocols for review, paying close attention to potential conflicts of interest, the scientific

content of the protocol, the potential reviewer's area of expertise, and representation for vulnerable populations that may be involved in the research. A primary reviewer will be assigned to protocols requiring initial review, continuing review, and review of proposed modifications. When the IRB is presented with a protocol which may be outside the expertise of the IRB members, an outside consultant will be sought (See *Section 2.8*). Protocols for which appropriate expertise cannot be obtained for a given meeting will be deferred to another meeting when that expertise and critique can be provided.

The primary reviewer is responsible for:

- Having a thorough knowledge of the details of the proposed research.
- Performing an in-depth review of the proposed research.
- Leading the discussion of the proposed research at the convened meeting, presenting both positive and negative aspects of the research, and leading the IRB through the regulatory approval criteria (See *Section 3.6*).
- Making suggestions for changes to the proposed research, where applicable.
- Completing all applicable IRB reviewer checklists.

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

3.5.4 Pre-Meeting Distribution of Documents

All required materials need to be submitted 7 business days prior to the convened meeting for inclusion on the following IRB agenda. The meeting agenda will be prepared by the IRB Compliance Specialist, as necessary, with the assistance of the HRPP Director and distributed to the IRB members prior to the meeting. All IRB members will receive the review materials no later than 3 business days before the scheduled meeting, to allow sufficient time for review of the materials prior to the meeting. The meeting materials typically include:

- Meeting agenda;
- Meeting minutes;
- Applicable business items and audit findings;
- Appropriate continuing education materials; and
- Protocol review materials (See Section 3.5.5).

3.5.5 Materials received by the IRB

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

- Initial IRB Application Form,
- Protocol that outlines all of the study procedures and requirements,
- Proposed Consent/Parental Permission/Assent Form(s),
- Recruitment materials including advertisements intended to be seen or heard by potential subjects.

The primary reviewer receives and reviews, in addition to the above, (1) any relevant grant applications; and, (2) the Investigator's Brochure (when one exists). Additionally, for HHS-supported multicenter clinical trials, the primary reviewer should receive and review a copy of the HHS-approved sample informed consent document(s) (when one exists) and the complete HHS-approved protocol (when one exists).

The materials provided to the primary reviewer will also be provided to all IRB members with the exception of the grant application and the PI's Brochure. These materials will be available upon request.

If an IRB primary reviewer requires additional information to complete the review, they may contact the PI directly or may contact the IRB Office to make the request.

If an IRB member requires additional information, they may contact the IRB Office to make the request of the PI.

Reviewers will use the *Initial Protocol Review Checklist (HRPP-CHK-003)* as a guide to complete their review. Checklists completed by the Primary Reviewer will be kept with the IRB files.

3.5.6 Quorum

A quorum consists of a simple majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area. If interventional research involving an FDA-regulated article is involved, a physician must be part in the quorum.

At IRB meetings, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote. The IRB Chair, with the assistance of the IRB staff, will confirm that an appropriate quorum is present before calling the meeting to order and will be responsible to ensure that the IRB meeting remains appropriately convened. If a quorum is not maintained, either by losing a majority of the members, losing the non-scientific member or another required member, the IRB cannot take action or vote on regulatory determinations until the quorum is restored. The IRB Staff will document the time of arrival and departure for all IRB members and notify the IRB Chair if quorum is not present. The IRB Staff and/or IRB Chair will complete the *Convened IRB Meeting Quorum Worksheet (HRPP-WKS-001)* to determine and document that the convened IRB meeting is appropriately constituted and refer to this document to ensure the quorum is maintained. The worksheet will be kept with each respective meeting minutes. The minutes of the meeting will also document when an IRB member leaves, the reason for leaving and when the IRB member returns to the meeting room.

It is generally expected that at least one unaffiliated member and one member who represents the general perspective of participants, will be present at IRB meetings. The IRB may, on occasion, meet without this representation; however, this is the exception (i.e., generally no more than 2-3 meetings per year).

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

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

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

3.5.7 Meeting Procedures

The IRB Chair will call the meeting to order, once it has been determined that a quorum is present. The Chair will remind IRB members to recuse themselves from the final deliberations and vote by leaving the room when there is a conflict. The IRB will review and discuss the IRB Minutes from the prior meeting and determine if there are any revisions/corrections to be made. If there are no changes to be made, the Minutes will be accepted as presented and considered final. If it is determined that revisions/corrections are necessary, the Minutes will be amended. If the revisions/corrections are significant and the IRB members vote to have the revised Minutes reviewed at the next meeting, this will be added on to the next agenda.

The IRB reviews all submissions for initial and continuing review, as well as requests for modifications. The primary reviewer presents an overview of the research and leads the IRB through the regulatory criteria for approval in the *Initial Protocol Review Checklist (HRPP-CHK-004)*. In order for the research to be approved, it must receive the approval of a majority of the voting members present at the meeting.

It is the responsibility of the IRB Compliance Specialist to record the proceedings of the meeting and develop Minutes.

3.5.8 Guests

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

Ex-officio guests are individuals who, by virtue of their position and their role at VARI, may regularly attend IRB meetings. Ex-officio guests may include: the Compliance Director, General Counsel, Chief Operations Officer (IO) or the Director of Research. Ex-officio guests may fully participate in the IRB discussion and deliberations, but may not vote.

Other guests may be permitted to attend IRB meetings at the discretion of the IRB Chair and the HRPP Director. Guests, other than ex-officio guests, may not officially speak unless requested by the IRB Chair and must sign a *Van Andel Institute IRB Member Confidentiality Agreement.*

3.6 Criteria for IRB Approval of Research

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

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

3.6.1 Risk/Benefit Assessment

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

- Judge whether the anticipated benefit, either of new knowledge or of improved health for the research subjects, justifies asking any person to undertake the risks;

- Disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

The assessment of the risks and benefits of proposed research - one of the major responsibilities of the IRB - involves a series of steps:

- **Identify the risks** that are associated with the requirements of the research. In evaluating risks and benefits, the IRB should consider those risks and benefits that may result from the research (as distinguished from the risks of diagnostic treatments or therapies subjects would receive even in not participating in the research).
- **Determine whether the risks will be minimized** to the fullest extent possible by evaluating the necessity of procedures that impart risk and whether the data could be gained by procedures that are already being performed for diagnostic or treatment purposes or by alternative procedures that impart less risk;
- **Identify the probable benefits** to be derived from the research;
- **Determine whether the risks are reasonable in relation to the benefits** to subjects, if any, and assess the importance of the knowledge to be gained;
- **Ensure that potential** subjects **will be provided with an accurate and fair description** of the risks or discomforts and the anticipated potential benefits, whenever informed consent is required.

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

When following Department of Defense regulations, the definition of minimal risk based on the phrase, “ordinarily encountered in daily life or during the performance of routine physical or physiological examination or tests,” shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).

3.6.1.1 Scientific Review

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

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

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

3.6.2 Equitable Selection of Subjects

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

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

At the time of continuing review, the IRB will determine that the PI has followed the subject selection criteria that were originally set forth at the time of the initial IRB approval.

3.6.2.1 Recruitment of Subjects

The PI will provide the IRB with all recruitment materials to be used in identifying subjects including recruitment methods, advertisements, and payment arrangements. The first contact prospective study subjects make is often with a receptionist who follows a script to determine basic eligibility for the specific study. The IRB should assure the procedures followed adequately protect the rights and welfare of the prospective subjects. See *Section 3.7.6* for a discussion of IRB review of advertisements, *Section 3.7.7* for a discussion of IRB review of payments.

In studies where the research activities will be carried out at an external site(s), the VARI IRB will require the external IRB's approval for recruitment materials.

When following Department of Defense regulations and the research involves U.S. military personnel:

- 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.
- When research involves U.S. military personnel, limitations on dual compensation:
- Prohibit an individual from receiving pay of compensation for research during duty hours.
- U.S. military personnel may be compensated for research if the participant is involved in the research when not on duty.

- Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to $50 for each blood draw.
- Non-Federal persons may be compensated for research participation other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.

3.6.3 Informed Consent

The IRB will ensure that informed consent will be sought from each prospective subject or the subject's legally authorized representative (LAR), in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.20. In addition, the IRB will ensure that informed consent will be appropriately documented in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27. The IRB will ensure, as part of its review, that the information in the consent document & process is consistent with the protocol, and, when applicable, the HIPAA authorization. VARI IRB has a template consent document, *Informed Consent Document Template (HRPP-TEM-001).*

3.6.4 Safety Monitoring

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

The IRB reviews the safety monitoring plan and determines if it makes adequate provision for monitoring the reactions of subjects and the collection of data to ensure the safety of subjects, and to address problems that may arise over the course of the study. If a plan was not submitted, the IRB determines whether a plan is required, and, depending on the circumstances, what the plan should include. The overall elements of the monitoring plan may vary depending on the potential risks, complexity, and nature of the research study. The method and degree of monitoring needed is related to the degree of risk involved. Monitoring may be conducted in various ways or by various individuals or groups, depending on the size and scope of the research effort. These exist on a continuum from monitoring by the PI in a small, low risk study to the establishment of an independent data and safety monitoring board for a large clinical trial.

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

- Monitoring is commensurate with the nature, complexity, size and risk involved.
- Monitoring is timely. Frequency should be commensurate with risk. Conclusions are reported to the IRB.
- For low risk studies, continuous, close monitoring by the study PI or an independent individual may be adequate and in appropriate format, with prompt reporting of problems to the IRB, sponsor and regulatory bodies, as applicable.
- For an individual Safety Monitor, the plan must include:

- Parameters to be assessed;
- Mechanism to assess the critical endpoints and safety data at appropriate intervals in order to determine when to continue, modify, or stop a study
- Frequency of monitoring; and
- Procedures for reporting to the IRB.

- For a Data Safety Monitoring Board (DSMB), the plan must include:
  - The name of the DSMB;
  - Mechanisms, where appropriate, to ensure independence of the DSMB is from the sponsor;
  - Composition of the monitoring group: experts in all scientific disciplines are needed to interpret the data and ensure research subject safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease and treatment under study should be part of the DSMB or be available, as necessary;
  - Frequency, content and dissemination of meeting reports; and
  - The frequency and character of monitoring meetings (e.g., open or closed, public or private).

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

3.6.5 Privacy and Confidentiality

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

3.6.5.1 Definitions

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

Confidentiality - Methods used to ensure that information obtained by researchers about their subjects is adequately protected from inappropriate access and not improperly divulged.

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

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

3.6.5.2 Privacy

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

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

- Methods used to identify and contact potential subjects;
- Settings in which an individual will be interacting with an PI;
- Appropriateness of all personnel present for research activities;
- Methods used to obtain information about subjects and the nature of the requested information;
- Information that is obtained about individuals other than the "target subjects," and whether such individuals meet the regulatory definition of "human participant" (e.g., a subject provides information about a family member for a survey);
- How to access the minimum amount of information necessary to complete the study.

3.6.5.3 Confidentiality

Confidentiality and anonymity are not the same. If anyone, including the PI, can readily ascertain the identity of the subjects from the data, then the research is not anonymous and the IRB must determine if appropriate protections are in place to minimize the likelihood that the information will be inappropriately divulged. Note that the presence or absence of elements considered identifiers under HIPAA are not typically sufficient, in-and-of themselves, in considering whether the identity of subjects can be readily ascertained. For example, when the subject group is small and the level of detail in the data great, or when the subject group consists of individuals with a rare disorder or characteristic, the likelihood of identifying subjects from the data increases. Safeguards designed to protect confidentiality should be commensurate with the potential of harm from inappropriate or unintentional disclosure.

At the time of initial review and with any applicable amendments, the IRB assesses whether there are adequate provisions to protect subject confidentiality. The IRB does this through the evaluation of the methods used to obtain, record, share, and store information about individuals who may be recruited to participate in studies. The PI will provide the information regarding the procedures in place to protect the confidentiality of research data and sensitive information. Sensitive information is data or information, on any storage media or in any form or format, which requires protection due to the risk of harm that could result from inadvertent or deliberate disclosure, unauthorized access, misuse, alteration, or loss or destruction of the information. This information should be reviewed at the time of initial review through the completion of the IRB application forms, any necessary HIPAA authorization forms, research protocol, and/or other submitted applicable materials.

The PI will provide information regarding information security procedures and plans to address the protection of written and paper documents, other physical media (e.g. CDs, tapes), and electronic data and information including the use, maintenance, storage, and transmission of information. The IRB will review all information received from the PI and determine whether or not the confidentiality of research subjects is sufficiently protected. In some cases, the IRB may also require that a Certificate of Confidentiality be obtained to further protect research data (See *Section 19.1*).

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

Research regulated by the FDA must comply with the information security requirements of 21 CFR 11.

3.6.6 Vulnerable Populations

Certain individuals, by nature of their age or mental, physical, economic, educational, or other situation, may be at increased vulnerability to accept exposure to risks. At the time of initial review, the IRB will consider the scientific and ethical reasons for including vulnerable subjects in research. The IRB may determine and require that, when appropriate, additional safeguards are put into place for vulnerable subjects, such as those with diminished decision-making capacity.

For an extensive discussion about the IRB's review and approval process for individual vulnerable populations, please refer to *Section 8*.

3.7 Additional Considerations

3.7.1 Determination of Risk

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

3.7.2 Investigator Qualifications

The IRB reviews credentials, curriculum vitae, resumes, or other relevant materials to determine whether PIs and members of the research team are appropriately qualified to conduct the research.

3.7.3 Investigator Conflicts of Interest

It is VARI's policy to preserve public trust in the integrity and quality of research by minimizing actual or perceived conflict of interest (COI) in the conduct of research. Information regarding federal regulations and VARI policies, procedures, and training relevant to COI is available at www.vai.org.

All PIs and members of the research team are required to submit COI disclosures in accordance with *Financial Conflict of Interest Policy (COI-POL-001)*, *Conflict of Commitments Policy (COI-POL-002)*, and *Institutional Conflict of Interest Policy (COM-POL-009)*. The research application asks protocol-specific questions regarding PI and research team compliance with disclosure requirements, the

existence of possible non-financial conflicts, and whether or not any COI management plans are in place. The IRB staff provides the Compliance Director responsible for COI issues, who is also the HRPP Director, with summary information about the protocol and the responses to the protocol-specific questions. If a potential conflict exists, the Compliance Director notifies the IRB staff and follows the procedures described in the policies listed above. If it is determined that no conflict exists, or that due to the nature of the conflict or circumstances of the protocol a management plan is not necessary, a report stating that is provided to the IRB Specialist and subsequently shared with the IRB reviewers. As part of its review process, the IRB will make a final determination as to whether COI exists with regard to the research under review. If a COI requiring management is identified, a management plan is developed by the VAI Conflicts Committee (CC) and provided to the IRB along with a summary describing the nature and circumstances of the conflict. The IRB reviews the proposed management plan and may accept it as written, make additions to, or otherwise strengthen the management plan. The final IRB-approved management plan is provided to the PI, the Compliance Director/HRPP Director, and the PI's department chair or direct supervisor. Final IRB approval of a protocol cannot be given until an approved conflict of interest management plan that adequately protects the human subjects enrolled in the protocol is in place.

3.7.4 Institutional Conflicts of Interest

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

Institutional financial interests may be created by gifts, payments, royalty income, equity, and other benefits from or interests in for-profit organizations. Institutional financial interests also are created by financial and fiduciary interests of institutional officials.

VARI has established policies and procedures to identify, review, and manage institutional conflicts of interest and to ensure the independence of IRB review. This information can be located at www.vai.org, in *Institutional Conflict of Interest Policy (COM-POL-009).*

3.7.5 Significant New Findings

During the course of research, significant new knowledge or findings about research, the medication or test article, and/or the condition under study may develop. Upon awareness, the PI must report any significant new findings to the IRB as soon as possible, but no later than 10 business days. The IRB will review these new findings with regard to the impact on the subjects' rights and welfare. Since the new knowledge or findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the IRB may require, during the ongoing review process that the PI contact currently enrolled subjects to inform them of the new information. The IRB will communicate this to the PI. The consent document should be updated for enrollment of new subjects. Currently enrolled subjects may need to be informed in writing of this new information and affirm their desire to continue participation in the study.

3.7.6 Advertisements and Recruitment Materials

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

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

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

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

- Statements implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the protocol.
- Claims, either explicitly or implicitly, that the drug, biologic or device was safe or effective for the purposes under investigation.
- Claims, either explicitly or implicitly, that the test article was known to be equivalent or superior to any other drug, biologic or device.
- Using terms like “new treatment,” “new medication,” or “new drug” without explaining that the test article was investigational.
- Promising “free medical treatment” when the intent was only to say subjects will not be charged for taking part in the investigation.
- Emphasis on payment or the amount to be paid, such as bold type or larger font on printed media.
- The inclusion of exculpatory language.
- Advertisements will not include compensation for participation in a trial offered by a sponsor to involve a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

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

- The name and address of the clinical PI and/or research facility.
- The condition being studied and/or the purpose of the research.
- In summary form, the criteria that will be used to determine eligibility for the study.
- The time or other commitment required of the subjects.
- The location of the research and the person or office to contact for further information.
- A clear statement that this is research and not treatment.
- A brief list of potential benefits.

The IRB will use the *Advertisements and Recruitment Materials Checklist (HRPP-CHK-012)* in the review of each proposal for utilization of advertisement/recruitment material. The completed checklists will be kept with the IRB files.

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

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

3.7.7 Payments to Research Subjects

When research subjects receive payment for participation, the amount of compensation must be proportional to the risks and inconveniences posed by participation in the study. Payment for participation is not considered a research benefit.

Regardless of the form of remuneration, PIs must take care to avoid unduly influencing subjects.

PIs who wish to pay research subjects must include the amount and schedule of all payments as part of their IRB application. PIs should indicate the justification for such payment, including:

- Substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject;
- Provide a breakdown of payments into categories such as reimbursements for expenses, and compensation for time; and
- Substantiate that payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue pressure or coercion on the potential subject to volunteer for the research study.

The IRB must review both the amount of payment and the proposed method and timing of disbursement to assure that neither entails problems of coercion or undue influence. The IRB will use the *Payment and Non-monetary Gifts Checklist (HRPP-CHK-013)* in the review of payments to research subjects. The completed checklists will be kept with the IRB files.

Credit for payment should accrue and not be contingent upon the participant completing the entire study. The IRB does not allow the entire payment to be contingent upon completion of the study, unless the study is limited to a single visit/episode. Any amount paid as bonus for completion of the entire study should not be so great as to unduly influence subjects to remain in the study when they otherwise would have withdrawn.

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

If payment will meet or exceed $600.00 USD, the consent form must inform subjects that they will be asked to provide their Social Security Number and verification of U.S Citizenship or Permanent Resident Status to receive payment. In general, unless the study is sensitive in nature, VARI Finance Department requires identifying information to issue checks, cash, or gift certificates to subjects. For sensitive studies, only name and address are required by the Finance Department, but the PI is required to keep an identity key in a secure place.

Payments in exchange for referrals of prospective participants, sometimes referred to as "finder's fees" or "referral fees" are not permitted. In addition, payments or other incentives designed to accelerate recruitment that are tied to the rate or timing of subject enrollment, e.g., "bonus payments," are prohibited.

3.7.8 Non-Monetary Gifts and Incentives

Similar to financial incentives, non-monetary gifts or incentives can also present issues of undue influence or coercion.

If subjects will be provided with non-monetary gifts or tokens of appreciation, such as totes, books, toys, or other similar materials, the approximate retail value should be described to the IRB. The IRB must also be provided with a description, photo, or sample product to review.

Non-financial incentives such as extra credit for students and access to services or programs can also create situations that impact a potential subject's ability to fully and freely consider participation in research.

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

PIs should carefully structure incentives and methods of disbursement so that they do not unduly influence or coerce participation.

The IRB will use the *Payment and Non-monetary Gifts Checklist (HRPP-CHK-013)* in the review of non-monetary gifts and incentives to research subjects. The completed checklists will be kept with the IRB files.

3.7.9 State and Local Laws

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

3.8 Possible IRB Actions

Approval – The study is approved as submitted.

Approval with Comments or Recommendations - This action is taken when the IRB has determined that the criteria for approval are satisfied and the IRB provides the investigator with comments or recommendations that the investigator may wish to consider.

Approval with Conditions that Must Be Addressed – This action is taken when the IRB has determined that the criteria for approval are satisfied as long as the PI makes prescribed, specific changes to the protocol, consent, or study materials; provides confirmation of specific assumptions or

understandings on the part of the IRB regarding how the research will be conducted; and/or submits additional documents. For example, the IRB may require:

- Precise language changes to the protocol or consent such as specified wording changes or substitutions;
- Confirmation that the research excludes children;
- Submission of an ethics training certificate; or
- More substantive modifications to the protocol or consent process that must be within clearly stated parameters, such as a requirement to revise the protocol to indicate that consent of prospective subjects will be obtained at least one week prior to an investigational procedure.

For protocols reviewed at a convened IRB meeting, the required, prescribed revisions are agreed upon at the IRB meeting. For protocols reviewed under expedited review, the required revisions are designated by the expedited reviewer(s).

In order to receive approval for a protocol approved with conditions that must be addressed:

- The PI's response, the revised protocol materials and the previously submitted documents are provided to the IRB Chair or other qualified individual(s) designated by the IRB to review the investigator's response. The reviewer(s) verify that the prescribed changes have been made and the conditions have been satisfied. The approval date for the protocol is the date that the IRB took the action of "Approval with Conditions that Must Be Addressed". The date the conditions were determined to be satisfied is the effective date of approval ('final approval').
- As appropriate, the Chair or designated reviewer may request the full Board's review of the investigator's response.

Final approval will not be issued until all conditions are satisfied. An exception to this is allowed when the IRB stipulates that certain components of the research that meet the criteria for approval, may commence or continue while other components of the research that require modification cannot be initiated or continued until the outstanding issues are resolved and final approval is issued.

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

The Chair or designated reviewer's determination that the conditions for approval have been satisfied will be included in the IRB protocol file and the IRB members are notified via the next meeting agenda that the study has been approved.

Deferred – This action is taken when substantial modification or clarification is required (of the nature or amount that the IRB cannot specify exact changes or parameters), or insufficient information is provided to judge the protocol submission adequately (e.g., the risks and benefits cannot be assessed with the information provided). For example, a justification for use of placebo and withholding currently available treatment is required, or a greater than minimal risk protocol has no description of how the safety of the study will be monitored. IRB approval of the proposed research cannot occur until subsequent review of the investigator's response at the convened IRB meeting.

In order to receive approval for a deferred submission:

- **For full review** - the PI's response must be reviewed at a convened meeting of the IRB. The IRB members are provided with the PI's written response, the revised materials and any other relevant materials necessary for review.

- For studies that initially qualified for expedited review and where the expedited reviewer found that clarification was needed in order to determine whether the study is approvable, the PI's written response, the revised materials and any other relevant materials necessary for review is provided to the same IRB expedited reviewer(s) unless the original reviewer is no longer available. In this case the review is completed by the IRB Chair or other qualified individual(s) designated by the IRB Chair to conduct expedited review. The expedited reviewer's determination that the study has met the criteria for approval is documented in the protocol file.

The protocol application will not be approved until all issues are addressed to the satisfaction of the convened IRB or the expedited reviewer(s).

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

Disapproved – The IRB has determined that the research cannot be conducted at VARI or by employees or agents of VARI.

Approval in Principle – As per federal regulations, (45 CFR 46.118), there are two circumstances in which the IRB may grant approval required by a sponsoring agency without having reviewed all of the study procedures and consent documents. One is if study procedures are to be developed during the course of the research, but human subjects approval is required by the sponsoring agency. The other is if the involvement of human subjects depends on the outcomes of work with animal subjects. The IRB may then grant approval without having reviewed the, as yet, undeveloped recruitment, consent, and intervention materials. However, if the proposal is funded, the PI must submit such materials in sufficient time for IRB review, and secure IRB approval before recruiting human subjects into the study, or into any pilot studies or pre-tests. Approval in principle is granted to satisfy sponsoring agency requirements or to allow PIs to have access to funding to begin aspects of the project that do not involve human subjects.

3.9 Approval Period

At the time of initial review and at continuing review, the IRB will make a determination regarding the frequency of review of the research protocols. All protocols will be reviewed by the IRB at intervals appropriate to the degree of risk but no less than once per year. In some circumstances, such as when the research involves a high likelihood or severity of risks, when the research imparts significant risks without likelihood of direct benefit, or when the research population is especially vulnerable, a shorter review interval (e.g. semi-annually, quarterly, or after accrual of a specific number of subjects) may be required (see below). Or, for a new PI or a PI who has recently had a protocol suspended by the IRB due to regulatory concerns, an on-site review by a subcommittee of the IRB might be required or approval might be subject to an audit of study performance after a few months of enrollment, or after enrollment of the first few subjects. The meeting minutes will reflect the IRB's determination regarding review frequency and the reason for shorter review intervals.

For each initial or continuing approval, the IRB will indicate an approval period with specification of the expiration date. IRB approval is considered to have lapsed at midnight on the expiration date of the approval. For a study reviewed and approved by a convened IRB, the approval commences on the date of the convened IRB meeting. If a study reviewed by a convened IRB meeting is approved with conditions that must be addressed, the IRB can vote to assign a reviewer to assess the PI's response (see *section 3.8*). The expiration date of the initial approval period, is the date by which time the first continuing review must occur. For a study approved under expedited review, the approval period begins on the date the IRB Chair or Chair designee(s) gives final approval to the protocol.

The approval date and approval expiration date are clearly noted on all IRB approval letters sent to the PI. PIs should allow sufficient time for development and review of renewal/continuing review submissions.

Review of a change in a protocol ordinarily does not alter the date by which continuing review is required to occur. This is because continuing review must be conducted by review of the full protocol and any results to date.

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur no later than midnight of the date when IRB approval expires.

3.10 Continuing Review

To assist PIs, the IRB Office staff will send out renewal notices to PIs two months and one month in advance of the expiration date. However, it is the PI's responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date. By federal regulation, no extension to that date can be granted.

PIs must submit the following for continuing review:

- The *Initial IRB Application Form (HRPP-FORM-001)* updated with any changes (this includes and serves as the protocol summary);
- The current protocol;
- The current consent document;
- The current PI's Brochure (if applicable);
- The most recent report from the DSMB or DMC (if applicable);
- The most recent multi-center progress report (if applicable);
- Any proposed modifications to the protocol, consent, or study; and
- The Continuing Review Progress Report Form (HRPP-FORM-004).

IRB staff attends the convened meetings and brings the complete protocol file for each protocol on the agenda. IRB members can request the protocol file or any additional materials prior to the meeting, or request to review the file while at the IRB meeting.

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

When following Department of Defense (DoD) regulations, the following shall be promptly reported to the DoD human research protection officer (HRPO) within 30 days):

- When significant changes to the research protocol are approved by the IRB.
- The results of the IRB continuing review.
- Change of reviewing IRB.

- When the organization is notified by any Federal department, agency or national organization that any part of the HRPP is under investigation for cause involving a DoD-supported research protocol.

3.10.1 Key Considerations

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

- Risk assessment and monitoring;
- Adequacy of informed consent;
- Local Principal Investigators (PI) and institutional issues; and
- Research progress.

3.10.2 Full Board Review

In conducting continuing review of research not eligible for expedited review, all IRB members are provided with access to all of the above materials and are responsible for reviewing the project summary, the current consent document, the progress report, and, if applicable, the data and safety monitoring report, multi-center study progress reports, and any proposed amendments to the research plan, protocol, or consent. The primary reviewer is responsible for reviewing the materials submitted for continuing review including the complete protocol and is given access to the IRB file and relevant IRB meeting minutes. At the meeting, the primary reviewer leads the IRB through the completion of the regulatory criteria for approval in the *Initial Protocol Review Checklist (HRPP-CHK-004)* and/or *Continuing Review Checklist (HRPP-CHK-003)*.

During the continuing review of research, the consent document (currently approved or newly proposed) must be reviewed, In addition, it should be noted that consent documents are reviewed whenever new information becomes available that may require modification of information in the consent document.

3.10.3 Expedited Review of Continuing Review

In conducting continuing review under expedited review, the designated IRB member receives all of the above material. The reviewer completes the *Initial Protocol Review Checklist (HRPP-CHK-004)* and/or *Continuing Review Checklist (HRPP-CHK-003)* to determine whether the research meets the criteria that allow continuing review using the expedited procedure, and if so, whether the research continues to meet the regulatory criteria for approval.

If the research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9). It is also possible that research activities that previously qualified for expedited review in accordance with 45 CFR 46.110, have changed or will change, such that expedited IRB review would no longer be permitted for continuing review.

3.10.4 Possible IRB Actions

As with Initial Review, at the time of Continuing Review, the convened IRB or IRB member conducting expedited review may take any of the following actions (See *Section 3.8* for a detailed description of these actions):

- Approval
- Approval with Comments or Recommendations
- Approval with Conditions that Must be Addressed
- Deferred

Additionally, if the IRB has significant concerns, the IRB may vote to suspend or terminate the research (See *Section 5* for a detailed discussion of suspensions and terminations).

If a research protocol is "Approved with Conditions that Must Be Addressed" at the time of the Continuing Review, the IRB will specify any restrictions or requirements that must be adhered to, until the conditions for approval have been satisfied. For example, if at the time of continuing review, the IRB determines that an additional screening procedure is necessary, the IRB could approve the research with conditions that must be addressed and specify that no new subjects may be screened and enrolled until the PI submits the revised protocol and the condition has been determined to be satisfied. Additionally, the IRB may specify a time period, such as 1, 2, or 3 months, for the condition to be satisfied.

3.10.5 Lapses in Continuing Review

The regulations permit no grace period or extension of approval date after the specified approval expiration. Research that continues after the approval period has expired is research conducted without IRB approval. If the continuing review does not occur within the timeframe set by the IRB, all research activities must stop, including recruitment (media advertisements must be pulled), enrollment, consent, interventions, interactions, and data collection, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. This will occur even if the PI has provided the continuing review information before the expiration date. Therefore, PIs must allow sufficient time for IRB review before the expiration date.

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

If research subjects are currently enrolled in the research project and their participation is ongoing, once notified of the expiration of approval, the PI must immediately submit to the IRB Chair a list of research subjects for whom suspension of the research would cause harm and a proposal describing and justifying the specific research procedures that should continue in order to avoid harm. Enrollment of new subjects cannot occur and continuation of research interventions or interactions for already enrolled subjects should only continue when the IRB or IRB Chair finds that it is in the best interest of the individual subjects to do so. If there is insufficient time to obtain approval from the IRB to continue subjects on a lapsed study, the PI can make an initial determination that study activities must continue due to safety of the subjects and promptly inform the IRB.

It should be noted that if the IRB notes a pattern of non-compliance with the requirements for continuing review (e.g., an investigator repeatedly or deliberately neglects to submit materials for continuing

review in a timely fashion, the IRB may determine that such a pattern represents serious or continuing noncompliance that will be handled according to the non-compliance policy (See *Section 12*).

Once approval has expired, IRB review and re-approval must occur prior to re-initiation of the research. If the study approval has lapsed, the PI must submit a continuing review report and the PI's department chair will be notified of this lapse.

3.11 Amendment of an Approved Protocol

PIs may wish to modify or amend their approved applications. PIs must seek IRB approval before implementing any changes in currently approved research, unless the change is necessary to eliminate any apparent immediate hazard(s) to the subject(s) or others (in which case the IRB must be notified immediately).

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

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

- Completed Protocol Modification Request Form (HRPP-FORM-003),
- Revised protocol, an updated Initial IRB Application Form (HRPP-FORM-001) (as appropriate), and/or study materials (with tracked changes, with a detailed summary and justification for the changes);
- Revised consent/parental permission/assent documents (if applicable) or other documentation to be provided to subjects when the proposed change(s) to the research might relate to their willingness to continue to participate in the study; and
- Any other relevant documentation provided by the sponsor or coordinating center.

IRB Office staff will review the submission and make an initial determination regarding whether the proposed changes may be approved through an expedited review process, if the changes are minor, or whether the modification warrants full board review. The reviewer using the expedited procedure has the ultimate responsibility to determine that the proposed changes may be approved through the expedited review procedure and, if not, will refer the protocol for full board review.

When following Department of Defense (DoD) regulations, the following shall be promptly reported to the DoD human research protection officer (HRPO) within 30 days):

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

3.11.1 Full Board Review of Protocol Modifications

When a proposed change in a research study is not minor, the IRB must review and approve the proposed change at a convened meeting before the modification can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB should be promptly informed of the modification, and a justification provided following its implementation. The IRB Chair or designee will review the change to determine that it is consistent with ensuring the subjects' continued health and welfare. This modification will be placed on the next IRB agenda for full review.

All IRB members are given a copy of all documents provided by the PI as part of their review responsibility.

At the meeting, the primary reviewer presents an overview of the proposed modifications and leads the IRB through the completion of the regulatory criteria for approval. The IRB will determine whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

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

3.11.2 Expedited Review of Protocol Modifications

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

The reviewer(s) complete the *Protocol Modification Checklist (HRPP-CHK-004)* and/or *Continuing Review Checklist (HRPP-CHK-003)* to determine whether the modifications meet the criteria for using the expedited review procedure, and if so, whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

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

3.11.3 Possible IRB Actions

As with Initial Review, at the time of Continuing Review, the convened IRB or IRB member(s) conducting expedited review may take any of the following actions (see *section 3.8* for a detailed description of these actions):

- Approval
- Approval with Comments or Recommendations
- Approval with Conditions that Must Be Addressed
- Deferred

Additionally, the convened IRB may vote to disapprove the proposed changes. If an IRB member conducting expedited review believes that the proposed modifications should be disapproved, they will

refer the amendment to the convened IRB for review. If the proposed changes raise significant concerns on the part of the IRB, the IRB may vote to suspend or terminate the research (See *Section 5)* for a detailed discussion of suspensions and terminations).

3.12 Closure of Protocols

The completion or termination of the study, whether premature or not, is a change in activity and must be reported to the IRB. Although subjects will no longer be "at risk" under the study, a closure 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.

Studies may be closed when the involvement of human subjects ceases (interventions, interactions, observations, and the gathering, use, study, and analysis of identifiable private information [including specimens] are all complete). An example of this is when the only remaining research activity involves the analysis of aggregate data sets without individual subject identifiers.

For multi-center research, the study may be closed once all local research activities (as above) are complete. If the PI is serving as the lead PI or VARI is the coordinating center, the study must remain open as long as the coordinating center is still receiving, studying, using, or analyzing identifiable private information from other sites (even if local interventions, interactions, observations, and data gathering is complete).

PIs may submit study closures to the IRB as part of the Continuing Review Report Form (HRPP-FORM-004). With the submission, the PI must provide a summary of the research activity and any findings.

PIs may maintain the data that they collected, including identifiable private data, if this is consistent with the IRB-approved research plan. PIs must continue to protect the confidentiality of the data as described to the IRB and honor any other commitments that were agreed to as part of the approved research including, for example, future use of data or specimens, provision of research results to subjects, and provision of any outstanding payments or compensation.

The IRB will review study closure reports, typically by expedited review, and either approve the closure of the study, request additional information or confirmation from the PI.

3.13 Reporting IRB Actions

All IRB actions are communicated to the PI, and designated primary contact person for the protocol, in writing within ten (10) business days via a letter prepared by the IRB staff that is reviewed and signed by the IRB Chair or Chair designee. For approval of a study, along with written notification of approval, a copy of the approved consent form (if applicable), indicating approval period on each page of the consent form will be sent to the PI.

For approval with conditions that must be addressed, the notification will include a list of the contingencies that must be satisfied in order for the research to be approved.

For a deferral, the notification will include the modifications and/or clarifications necessary along with the basis for requiring those modifications.

For a disapproval, termination or suspension, the notification will include the basis for making that decision.

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

The IRB reports its findings and actions to the institution in the form of its minutes, which are distributed by IRB Office staff to the VARI Institutional Official, as requested, and are stored permanently and securely in the IRB Office.

3.14 Appeal of IRB Decisions

When an IRB protocol is disapproved or deferred, the IRB will notify the PI in writing about the specific deficiencies and the modifications that are necessary in order to obtain IRB approval. The IRB shall include in its written notification a statement the reasons for its decision and give the PI an opportunity to respond in writing. Similarly, when research is suspended, in part or in full, or terminated, the IRB will notify the PI in writing of the suspension or termination and the reasons for its decision.

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

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

4 Quality Assurance

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

4.1 Independent Verification That No Material Changes Have Occurred

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

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

- Protocols where concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources;
- Protocols conducted by PIs who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB;
- Complex projects involving unusual levels or types of risk to subjects; and
- Whenever else the IRB deems verification from outside sources is necessary.

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

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken.

4.2 Consent Monitoring

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

Such monitoring may be particularly warranted for:

- High risk studies;
- Studies that involve particularly complicated procedures or interventions;
- Studies involving highly vulnerable populations (e.g., ICU patients, children);

- Studies involving study staff with minimal experience in administering consent to potential study subjects; or
- Other situations when the IRB has concerns that the consent process is not being conducted appropriately.

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

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

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

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

4.3 Data Monitoring Reports

Reports describing the outcome of ongoing safety monitoring (such as DMC or DSMB reports) must be submitted to the IRB in a timely manner (typically within 15 business days after receipt). In the event the report recommends modifications to the research or suspension or termination of some or all research activities due to safety concerns, the IRB office should be contacted and the monitoring report submitted immediately.

4.4 External Monitoring, Audit, and Inspection Reports

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

The HRPP Director should be notified in advance of upcoming audits or inspections, whenever possible.

4.5 PI Compliance Reviews

The HRPP Director is responsible for, but can delegate, random post-approval audits and for-cause audits of protocols. Additionally, the IRB may appoint a subcommittee for the purpose of conducting compliance review audits of one or more protocols under its jurisdiction. The subcommittee may be composed of IRB members and staff from within and outside the organization.

Compliance reviews are conducted to assess PI compliance with federal, state, and local laws, and VARI policies, to identify areas for improvement, and to provide recommendations based on existing policies and procedures. The results of compliance reviews will be reported to the HRPP Director, the IRB, and the PI. Any non-compliance will be handled according to the procedures in *Section 12*.

If it is identified that subjects in a research project have been potentially exposed to unexpected serious harm, the reviewer will promptly report such findings to the HRPP Director and the IRB Chair for immediate action.

If issues are identified that indicate possible misconduct in research, the procedures called for in the *COM-POL-002.01 Research Misconduct* will be initiated.

Compliance reviews may include:

- Requesting progress reports from researchers;
- Examining PI-held research records;
- Contacting research subjects;
- Observing research sites where research involving human research subjects and/or the informed consent process is being conducted;
- Reviewing advertisements and other recruitment materials;
- Reviewing projects to verify from sources other than the researcher that no unapproved changes have been implemented since the previous review;
- Monitoring COI concerns to assure adherence to the approved management plan (e.g., related to the protocol and consent document)
- Monitoring HIPAA authorizations; and
- Conducting other monitoring or auditing activities as deemed appropriate by the HRPP or IRB.

4.6 IRB Compliance Reviews

The HRPP Director, or delegated individual, may require assistance of an outside consultant or organization. The HRPP Director will periodically review the activities of the IRB to assess compliance with regulatory requirements to identify areas of potential improvement. This will include a partial review of IRB records at least annually. Review activities may also include:

- Review of the IRB minutes to determine that adequate documentation of the meeting discussion has occurred. This review will include assessment of the documentation surrounding the discussion for protection of vulnerable populations as well as other risk/benefit related issues and consent issues that are included as part of the criteria for approval;
- Review of the IRB minutes to assure that quorum was met and maintained;
- Review of IRB documentation, including IRB minutes, to assess whether privacy provisions, according to HIPAA, have been adequately reviewed, discussed and recorded;
- Evaluation of the continuing review discussions to assure they are substantive and meaningful and that no lapse has occurred since the previous IRB review;
- Review of the IRB files to assure retention of appropriate documentation and consistent organization of the IRB file according to current policies and procedures;
- Review of the IRB database to assure all fields are complete and accurate;
- Verification of IRB approvals for collaborating institutions or external performance sites;
- Assessment of review timelines (metrics), e.g., time from submission to first review, to evaluate the quality, efficiency, and effectiveness of the IRB review process;
- Review of the workload of IRB staff to evaluate appropriate staffing level; and
- Other monitoring or audit activities deemed appropriate by the IRB.

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

4.7 HRPP Quality Assessment and Improvement

Quality Assurance reports, including compliance reviews, are reviewed by the HRPP Director with the IO available for consultation, in order to identify trends and to determine if systemic changes are required to prevent re-occurrence. If so, the HRPP Director and other relevant parties such the IO, the IRB Chair, the IRB Compliance Specialist, will collaborate in the development of a corrective action plan, its implementation, and evaluation of its effectiveness.

The IRB Compliance Specialist is responsible for tracking internal metrics that are informative in consideration of IRB and PI efficiencies, such as the amount of time from receipt of a submission through pre-review, assignment to the IRB agenda, final approval, and the amount of time it takes PIs to develop and submit responses to post-IRB review requirements and determinations. Metric reports will be provided to the HRPP Director and IRB Chair and Vice Chair twice per year.

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

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

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

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

5 Study Suspension, Termination and Investigator Hold

5.1 Suspension/Termination

IRB approval may be suspended or terminated if research is not being conducted in accordance with IRB or regulatory requirements or has been associated with unexpected problems or serious harm to subjects. (See *Section 10* for a discussion of unexpected problems and *Section 12* for a discussion of non-compliance)

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

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

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

When study approval is suspended or terminated by the convened IRB or an authorized individual, in addition to stopping all research activities, the convened IRB or individual ordering the suspension or termination will consider notification of subjects and any actions necessary to ensure the rights, safety, and welfare of subjects.

PIs are required to continue to provide reports on adverse events and unanticipated problems to both the IRB and sponsor despite the suspension. All events that need to be reported during a study must continue to be reported during the suspension period.

Suspension or termination of protocols approved by the IRB can also be issued by VARI officials acting outside of and unrelated to the interests of the IRB (i.e., not necessarily related to protecting the rights and welfare of study subjects). Such VARI actions can be made by the VAI Chairman and Chief Executive Officer, VARI General Counsel, Director of Research and Chief Scientific Officer or IO. The PI must report any suspension or termination of the conduct of research by VARI officials to the IRB. The IRB will review the circumstances to determine the impact of the suspension on the study and on the research subjects. The IRB will then determine if suspension or termination of IRB approval is warranted and any actions necessary to notify or to protect human subjects.

5.2 Investigator Hold/Administrative Hold

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

5.2.1 Procedures

PIs must notify the IRB in writing that he/she is:

- Voluntarily placing a study on administrative hold;
- Providing description of the research activities that will be stopped;
- Proposing actions to be taken to protect current subjects;
- Indicating the actions that will be taken, prior to IRB review of proposed changes, in order to eliminate apparent immediate harm;

Upon receipt of written notification of the PI, the IRB Compliance Specialist places the research on the agenda for review;

The IRB Chair, Vice Chair, and/or HRPP Director, in consultation with the PIs, determine whether any additional procedures need to be followed to protect the rights and welfare of current subjects as described in S*ection 5.3* below.

The IRB Chair, Vice Chair, and/or HRPP Director, in consultation with the PIs, will determine whether, and if so, how and when currently enrolled subjects will be notified of the administrative hold.

PIs may request a modification of the administrative hold by submitting the *Protocol Modification Request Form (HRPP-FORM-003).* This modification request must be approved prior to re-opening the study.

5.3 Protection of Currently Enrolled Subjects

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

- Transferring subjects to another PI;
- Making arrangements for clinical care outside the research;
- Allowing continuation of some research activities under the supervision of an independent monitor;
- Requiring or permitting follow-up of subjects for safety reasons;
- Requiring adverse events or outcomes to be reported to the IRB and the sponsor;

- Notification of current subjects; and
- Notification of former subjects.

6 Documentation and Records

VARI prepares and maintains adequate documentation of the IRB's activities. All records are accessible for inspection and copying by authorized representatives of the FDA, OHRP, sponsors, and other authorized entities at reasonable times and in a reasonable manner. When following Department of Defense (DoD) regulations, records maintained that document compliance or non-compliance with DoD requirements shall be made accessible for inspection and copying by representatives of the DoD at reasonable times and in a reasonable manner as determined by the supporting DoD component.

6.1 IRB Records

IRB records include, but are not limited to:

- Written operating procedures;
- IRB membership rosters;
- Training records: documenting that researchers, IRB members, and IRB staff have fulfilled VARI's human subject training requirements;
- IRB correspondence including reports to regulatory agencies;
- IRB Protocol Records (Study Files) including correspondence with PIs and research team;
- Documentation of exemptions;
- Documentation of convened IRB meeting minutes;
- Documentation of review by another institution's IRB, when appropriate;
- Documentation of cooperative review agreements (e.g. Memoranda of Understanding (MOUs);
- Federal Wide Assurances;
- IRB Registrations; and
- Documentation of complaints and any related findings and/or resolution.

6.2 IRB Study Files

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

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

- Protocol and all other documents submitted as part of a new protocol application;

- Protocol and all other documents submitted as part of a request for continuing review, progress reports, or closure of research;
- Documents submitted and reviewed after the study has been approved, including amendment requests, protocol exception requests, proposed advertisements, data and safety monitoring reports, and reports of protocol violations, complaints, non-compliance, unanticipated device events and unanticipated problems;
- Copy of IRB-approved Consent Form;
- DHHS-approved sample consent form document and protocol, when they exist;
- IRB reviewer forms;
- Documentation of scientific review (if available);
- Documentation of type of IRB review. For exempt determinations and expedited review, this will include the category under which the review is allowed;
- For expedited review, IRB records document the name of the person reviewing the expedited protocol, and documents any determinations required by the regulations and protocol-specific findings supporting those determinations, including: waiver or alteration of the consent process, research involving pregnant women, fetuses, and neonates, research involving prisoners, and research involving children. IRB records include documentation that the reviewer determined that the research involves no more than minimal risk and a determination of the frequency of continuing review for each study. For research reviewed by the convened board, these determinations are recorded in the minutes;
- For exempt research records document the name of the person making the exempt determination;
- Documentation of all IRB review actions;
- Notification to the PI of expiration of IRB approval and requirements related to the expiration;
- Notification of suspension or termination of research;
- Copies of approval letters and forms that describe any requirements that the PI must satisfy before beginning the study;
- IRB correspondence to and from the PI;
- All other IRB correspondence related to the research;
- For devices, documentation of determination by IRB of significant risk, non-significant risk, or exempt;
- Reports of unanticipated problems involving risk to subjects or others, reports of injuries to subjects, and unanticipated adverse events;
- Significant new findings provided by the investigator or discovered through others means. The IRB determines if statements of significant new findings should be provided to subjects.

6.3 The IRB Minutes

Proceedings are written and available for review at a regularly scheduled IRB meeting. Once approved by the members at a subsequent IRB meeting, the minutes cannot be altered by anyone, including a higher institutional authority.

A copy of IRB-approved minutes for each IRB meeting will be distributed to the IO, as requested.

Minutes of IRB meetings must contain sufficient detail to show:

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

   [Note: The attendance list shall include those members present at the meeting. The minutes will indicate, by name, those members who enter or leave the meeting. The vote on each action will reflect the numbers of members present for the vote on that item. Members who recuse themselves because of conflict of interest are listed by name and the reason documented, if available.]
8. The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area.
9. Business items discussed and any in-service education provided.
10. Actions taken, including separate deliberations, actions, and votes for each protocol undergoing review by the convened IRB.
11. Vote counts on these actions (Total Number Voting; Approve (number voting for); Disapprove (number voting against); Abstain (number abstaining); Recused (number of members recused).
12. Basis or justification for actions related to disapproval or requiring changes in research;
13. Summary of controverted issues and their resolution.
14. Approval period for initial and continuing approved protocols, including identification of research that warrants review more often than annually and the basis for that determination.

15. Risk level of initial and continuing approved protocols.
16. Justification for deletion or substantive modification of information concerning risks or alternative procedures contained in the HHS-approved sample consent document.
17. Protocol-specific findings supporting that the research meets each of the required criteria when approving a consent procedure that does not include or that alters some or all of the required elements of informed consent, or when waiving the requirement to obtain informed consent altogether.
18. Protocol-specific findings supporting that the research meets each of the required criteria when the requirements for documentation of consent are waived.
19. Protocol-specific findings supporting that the research meets each of the criteria for approval under any applicable Subparts. This includes 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.
20. The rationale for significant risk/non-significant risk device determinations.
21. Determinations of conflict of interest and acceptance or modification of conflict of interest management plans.
22. Identification of any research for which there is need for verification from sources other than the PI that no material changes have occurred in the research.
23. A list of research approved since the last meeting utilizing expedited review procedures.
24. An indication that, when an IRB member or alternate member has a conflicting interest (see Section 2.7) with the research under review, the IRB member or alternate member was not present during the final deliberations or vote, and that the quorum was maintained.
25. Key information provided by consultants will be documented in the minutes or in a report provided by the consultant.
26. Determinations made by the convened IRB related to the review of non-compliance, protocol deviations, unanticipated problems involving risks to participants or others, serious adverse events, suspensions and terminations, and complaints.
27. Discussion of statements of any significant new findings provided by the investigator.

6.4 IRB Membership Roster

A membership list of IRB members must be maintained; and must contain the following information:

- Name;
- Earned degrees;
- Employment or other relationship (affiliated or non-affiliated) between each member and VARI - neither the member nor an immediate family member of the IRB member may be affiliated with VARI;

- Status as scientist or non-scientist. Members whose training, background, and occupation would incline them to view scientific activities from the standpoint of someone within a behavioral or biomedical research discipline are considered a scientist for the purposes of the roster, while members whose training, background, and occupation would incline them to view research activities from a standpoint outside of any biomedical or behavioral scientific discipline are considered a nonscientist;
- Indications of experience, such as board certifications or licenses sufficient to describe each member's chief anticipated contributions to IRB deliberations;
- Representative capacities of each IRB member; at a minimum which IRB members are knowledgeable about or experienced in working with children, pregnant women, cognitively impaired individuals, prisoners and other vulnerable populations, as appropriate; Role on the IRB (Chair, Co-Chair, etc.);
- Voting status;
- For alternate members, the primary member or class of members for whom the member could substitute.

The IRB office must keep the IRB membership list current. The HRPP Director or designate will report changes in IRB membership to the OHRP, HHS within 90 days of the change.

6.5 Documentation of Expedited Reviews

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

- Approving a procedure which waives or alters the informed consent process;
- Approving a procedure which waives the requirement for documentation of consent;
- Approving research involving pregnant women, human fetuses, or neonates;
- Approving research involving prisoners; and
- Approving research involving children.

6.6 Access to IRB Records

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

- All IRB records are kept secure within the IRB Offices. The IRB files are locked when the office is unattended;
- Ordinarily, access to all IRB records is limited to the HRPP Director, IRB Chair, IRB members, IRB Office staff, authorized institutional officials, and officials of Federal and state regulatory agencies (OHRP, FDA). PIs are provided reasonable access to files related to their own research. Appropriate accreditation bodies are provided access and may

recommend additional procedures for maintaining security of IRB records. All other access to IRB records is limited to those who have legitimate access needs , as determined by the IO and HRPP Director;

- Records are accessible for inspection and copying by authorized representatives of Federal regulatory agencies during regular business hours;
- Records may not be removed from the IRB Office; however, the IRB staff will provide copies of records for authorized personnel, if requested; and
- All other access to IRB study files is prohibited.

6.7 Record Retention

In order to comply with the requirements of OHRP, FDA, and HIPAA, IRB records are maintained at the facility for at least seven (7) years after completion of the research.

IRB records not associated with research or for protocols cancelled without participant enrollment will be retained at VARI for at least 3 years after closure.

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

7 Obtaining Informed Consent from Research Subjects

No PI conducting research under the auspices of VARI may involve a human being as a subject in research without obtaining the legally effective informed consent of the subject or the subject's legally authorized representative (LAR) unless a waiver of consent has been approved by the IRB in accordance with *Section 7.9* of these procedures. Except as provided in *Sections 7.10* and *7.11* of these procedures, informed consent must be documented by the use of a written consent form approved by the IRB.

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

The following procedures describe the requirements for obtaining consent from subjects in research conducted under the auspices of VARI.

7.1 Definitions

Legally Authorized Representative (LAR). A LAR is an individual authorized under applicable law to provide permission on behalf of a prospective subject to the subject's participation in the research. For the purposes of this policy, a LAR includes a person appointed as a health care agent under a Durable Power of Attorney for Health Care (DPAHC) or as patient advocate under a Patient Advocate Designation, a court appointed guardian of the person, and next-of-kin in the following order of priority: spouse, adult child, parent, adult relative with whom the person has been residing for the previous 6 months. The order of priority of a LAR is: court ordered representative, then patient advocate designation, then the above-stated priority of next-of-kin.

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

7.2 Basic Requirements

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

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

Informed consent is more than just a signature on a form. It is a process of information exchange to include reading and signing the informed consent document. The informed consent process is a critical communication link between the prospective human subject and the PI, beginning with the initial recruitment approach and continuing through the completion of the research study. PIs must have received the appropriate training in the informed consent requirements and processes and be knowledgeable about the study protocol in order that they may answer questions to promote an understanding of the study to the potential study subject. The exchange of information between the PI and study subject can occur via one or more of the

following modes of communication; face-to-face contact, mail, telephone, video-conferencing, or fax. Obtaining informed consent must allow for a dialogue so that the potential subject has the opportunity to ask questions and have their questions answered to their satisfaction. PIs must obtain consent prior to enrolling a subject into a study and prior to initiating any procedures required by the protocol, unless consent is waived by the IRB.

If someone other than the PI will obtain consent from a potential subject, the PI needs to formally delegate this responsibility and obtain IRB approval for this delegation. The person approved to obtain consent must have had the appropriate training on how to obtain consent, the consenting process, must be knowledgeable about the research to be conducted, and must be able to answer any question about the study.

In requesting approval to delegate consenting responsibilities, the PI must provide an explanation of how the proposed consenting individual has been trained to obtain consent by addressing the following:

- What qualifies this individual to obtain consent;
- What specific training has this individual had or will this individual have to assure that he/she knows the protocol and can answer any question posed by potential subjects; and
- What ongoing supervision/training will be provided for this individual?

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

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

7.3 Informed Consent Process

Informed consent must be obtained under the following circumstances:

- Informed consent may only be obtained from subjects who have the legal and mental capacity to give consent. For subjects without that capacity, consent must be obtained from a legal guardian or LAR.
- The informed consent process provides the prospective subject (or LAR) with sufficient opportunity to read the consent document, when applicable.
- The informed consent process shall be sought under circumstances that provide the subject (or LAR) with sufficient opportunity to consider whether or not to participate.
- The informed consent process shall be sought under circumstances that minimize the possibility of coercion or undue influence.
- The informed consent information must be presented in language that is understandable to the subject (or LAR). To the extent possible, the language should be understandable by a person who is educated to the 8th grade level and layman's terms shall be used in the description of the research, per the informed consent process.

- For subjects whose native language is not English, informed consent must be obtained in a language that is understandable to the subject (or the subject's LAR). In accordance with this policy, the IRB requires that informed consent conferences include a reliable translator when the prospective subject does not understand the language of the person who is obtaining consent.
- The informed consent process may not include any exculpatory language through which the subject is made to waive, or appear to waive any of the subject's legal rights or through which the PI, the sponsor, VARI or VARI employees or agents are released or appear to be released from liability for negligence.
- The PI is responsible for insuring that each prospective subject is adequately informed about all aspects of the research and understands the information provided.

7.4 Determining a Potential Adult Subject's Ability to Consent to Research

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

- That the activity is research, not standard treatment
- Of the risks and benefits of the study
- Of the alternatives that are available if s/he does not participate
- That, if s/he chooses not to participate, this decision will be accepted without penalty, and will not jeopardize clinical care

In reaching a decision about participation, it is essential for the potential subject to demonstrate an ability to use this information in a rational manner. Thus, in considering risks, benefits, and available alternatives, subjects must show they understand the aspects of these factors that are unique to them as individuals. To highlight this distinction, a person who is suffering with severe depression may be able to demonstrate an understanding of a, b, c and d above, but may not care, or may actually want to put themselves at risk. Such individuals should not be considered able to provide consent for themselves.

For further discussion regarding adults who cannot consent for themselves, see *Section 8.10*.

7.5 Basic Elements of Informed Consent

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

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

- A disclosure of appropriate **alternative procedures** or courses of treatment, if any, that might be advantageous to the subject;
- A statement describing the extent, if any, to which **confidentiality** of records identifying the subject will be maintained;
- For research involving more than minimal risk, an explanation as to the availability of medical treatment in the case of **research-related injury**, including who will pay for the treatment and whether other financial compensation is available;
- An **explanation of whom to contact on the research team** for answers to pertinent questions about the research or to voice concerns or complaints about the research, and whom to contact in the event of a research-related injury to the subject;
- **Contact information for the IRB** to obtain answers to questions about the research; to voice concerns or complaints about the research; to obtain answers to questions about their rights as a research participant; in the event the research staff could not be reached; and in the event the subject wishes to talk to someone other than the research staff.
- A statement that participation is **voluntary**, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled;
- For **FDA-regulated studies**, the possibility that the Food and Drug Administration may inspect the records needs to be included in the statement regarding subject confidentiality.
- For **FDA-regulated clinical trials,** other than phase 1 clinical investigations of drugs or biological products, small feasibility trials of devices, and FDA-mandated pediatric post-market surveillance studies of devices, the following statement must be included verbatim:

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

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

1. A statement that the particular treatment or procedure may involve risks to the subject, which are currently unforeseeable. (For example: Include when the research involves investigational test articles or other procedures in which the risks to subjects is not well known.)
2. A statement that if the subject is or becomes pregnant, the particular treatment or procedure may involve risks to the embryo or fetus, which are currently unforeseeable. (For example: Include when the research involves pregnant women or women of childbearing potential and the risk to fetuses of the drugs, devices, or other procedures involved in the research is not well known.)
3. Anticipated circumstances under which the subject's participation may be terminated by the PI without regard to the subject's consent. (For example: Include anticipated circumstances under which the PI may terminate participation of a subject.)

4. Any additional costs to the subject that may result from participation in the research. (For example: Include information regarding additional costs that subject may incur.)
5. The consequences of a subject's decision to withdraw from the research. (For example: Include information that withdrawal from the research may be associated with adverse consequences.)
6. Procedures for orderly termination of participation by the subject. (For example: Include information when the protocol describes such procedures.)
7. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject. (For example: Include if interim information is likely to be developed during the conduct of the research.)
8. The approximate number of subjects involved in the study. (For example: Include when the research involves more than minimal risk.)

7.6 Documentation of Informed Consent

Except as provided in *Section 7.9* of this document, informed consent must be documented by the use of a written consent form approved by the IRB.

Informed consent is documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's LAR at the time of consent.

A copy of the signed and dated consent form must be given to the person signing the form. The PI should retain the signed original or a copy in the research records.

The consent form may be either of the following:

- A written consent document that embodies the basic and required additional elements of informed consent. The consent form may be read to the subject or the subject's LAR, but the subject or LAR must be given adequate opportunity to read the document before signing; or
- A short form written consent document stating that the elements of informed consent have been presented orally to the subject or the subject's LAR. When this method is used:
    - The oral presentation and the short form written document should be in a language understandable to the prospective subject;
    - There must be a witness to the oral presentation;
    - The IRB must approve a written summary of what is to be said to the prospective subject (the approved full consent document may serve as this summary);
    - The short form document is signed by the subject;
    - The witness must sign both the short form and a copy of the summary;
    - The person actually obtaining consent must sign a copy of the summary; and

- A copy of the summary must be given to the subject or LAR, in addition to a copy of the short form.

When this procedure is used with subjects who do not speak English, (i) the oral presentation and the short form written document should be in a language understandable to the prospective subject; (ii) the IRB-approved English language informed consent document may serve as the summary; and (iii) the witness should be fluent in both English and the language of the potential subject. When the person obtaining consent is assisted by a translator, the translator may serve as the witness.

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

7.7 Special Consent Circumstances

7.7.1 Non-English Speaking Subjects

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

Unexpected enrollment of a non-English speaking subject: If a non-English speaking subject is unexpectedly eligible for protocol enrollment, there may not be an extant IRB-approved written translation of the consent document. PIs should carefully consider the ethical and legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented at the signing of the consent document or in subsequent discussions, his/her consent may not be informed, and therefore, may not be effective. If this is the case, the subject should not be entered into the study.

If a PI decides to enroll a subject into a protocol for which there is not an extant IRB-approved informed consent document in the prospective subject's language, the PI must receive IRB approval to follow the procedures for a “short form” written consent in as described in *Section 7.6*.

Use of interpreters in the consent process: Unless the person obtaining consent is fluent in the prospective subject’s language, an interpreter is required to deliver information in the IRB-approved script and to facilitate the consent conversation. Someone who is independent of the subject (i.e., preferably not a family member) should assist in presenting information and be a

part of the consent process. Whenever possible, interpreters should be provided copies of the short form and the IRB-approved consent script well before (24 to 48 hours if possible) the consent conversation with the subject. If the interpreter also serves as the witness, she/he may sign the short form consent document and script as the witness and should note “Interpreter” under the signature line. The person obtaining consent must document that the “short form” process was used in the progress notes of the subject's medical record, including the name of the interpreter.

7.7.2 Braille consent

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

7.7.3 Consenting in American Sign Language (ASL)

For deaf subjects who are fluent in ASL, the IRB may approve a consent process using ASL and the IRB-approved written consent form. When this process is approved, the individual authorized to consent prospective subjects must use a certified interpreter fluent in ASL to conduct the consent process and the documentation of the consent process must conform to the requirements set forth in *Section 7.6*.

7.7.4 Oral Consent

When subjects are unable to read a written consent form (such as blind or illiterate subjects), the IRB may approve an oral consent process, provided the subject (1) has the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally and (2) is able to indicate whether he/she wants to enroll in the study.

For research that is no more than minimal risk, documentation of consent may be waived according to the criteria in *Section 7.10*.

For more than minimal risk research, the consent form must be read to the potential subject and the subject must be given an opportunity to ask questions. An audiotape approved by the IRB may be used and is strongly encouraged where possible. If capable, the subject signs, or marks an X to signify consent. If this is not possible, the potential subject will provide verbal consent. The person obtaining consent and a witness will sign the written study consent form with a statement that specifies that an oral process was used and that the subject gave verbal consent. The consent process will also be documented in the research record. Signed copies of the consent form are given to the subject and, whenever possible, these documents should be provided to the subject on audio or video tape.

7.8 Subject Withdrawal or Termination

For a variety of reasons, a subject enrolled in a research study may decide to withdraw from the research, or a PI may decide to terminate a subject's participation in research regardless of whether the subject wishes to continue participation. In these circumstances, questions sometimes arise about: (1) whether the PI may use, study, or analyze already collected data about the subject who withdraws from the research or whose participation is terminated by the PI; and (2) whether the PI can continue to obtain data about the subject and, if so, under what circumstances. PIs must plan for the possibility that subjects may withdraw from research and include a discussion of what withdrawal means and how it is to be handled in their research protocols and informed consent documents.

Regulatory requirements regarding the retention and use of data after subject withdrawal or termination differ between FDA regulations and research not subject to FDA regulations. Under applicable FDA law and regulations, data collected on human subjects enrolled in an FDA-regulated research up to the time of subject withdrawal must remain in the trial database in order for the study to be scientifically valid. For research not subject to FDA regulations, PIs, in consultation with the funding agency, can choose to honor a research subject's request that the PI destroy the subject's data or that the PI exclude the subject's data from any analysis.

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

- For FDA-regulated studies and clinical trials, when a subject withdraws from a study, the data collected on the subject to the point of withdrawal remain part of the study database and may not be removed. The consent document cannot give the subject the option of having this previously collected data removed.
- For research not subject to FDA regulations, the PI should inform subjects whether the PI intends to either: (1) retain and analyze already collected data up to the time of subject withdrawal; or (2) honor a research subject's request that the PI destroy the subject's data or (3) the PI exclude the subject's data from any analysis.

Sometimes, a subject wants to withdraw from the primary interventional component of a study, but is willing to allow the PI to continue other research activities described in the IRB-approved protocol and informed consent, such as: (1) obtaining data about the subject through interaction with the subject (e.g., through follow-up interviews, physical exams, blood tests, or radiographic imaging); or (2) obtaining identifiable private information from the subject's medical, educational, or social services agency records or from the subject's healthcare providers, teachers, or social worker. When a subject's withdrawal request is limited to discontinuation of the primary interventional component of a research study, research activities involving other types of participation for which the subject previously gave consent may continue. The PI should ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through noninvasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.

If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous paragraph, the

PI must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). IRB approval of informed consent documents for this purpose would be required.

If a subject (a) withdraws from the interventional portion of a study, (b) does not consent to continued follow-up of associated clinical outcome information, and (c) does not request removal of their data, the PI cannot access, for purposes related to the study, the subject's medical record or other confidential records requiring the subject's consent. However, a PI may review study data related to the subject that was collected prior to the subject's withdrawal from the study, and may consult public records, such as those that establish survival status.

7.9 Waiver of Informed Consent

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

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

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

- 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,
- The research could not practicably be carried out without the waiver or alteration.

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

7.10 Waiver of Documentation of Informed Consent

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

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

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

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

OR

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

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

In cases in which the documentation requirement is waived, the IRB requires the PI to provide in the application materials a written summary of the information to be communicated to the subject. The IRB will consider whether the PI is required to provide subjects with a written statement regarding the research. If a written statement is required, this document must be approved by the IRB.

8 Vulnerable Subjects in Research

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

In the event that VARI reviews research funded by the National Institute on Disability and Rehabilitation Research, when that 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 these research subjects.

The following procedures describe the requirements for involving vulnerable subjects in research under the auspices of VARI.

8.1 Definitions

Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. According to Michigan State Law, minors are persons under the age of eighteen. The general rule is that a person may consent for his or her own medical care at the age of eighteen. Therefore, VARI IRB generally defines children as persons under eighteen years of age. Certain statutes and case law, however, provide minors with "majority" status in some circumstances, giving them the right to consent to their own medical care. For example:

- Emancipated minors, Michigan law enumerates certain categories of individuals who, although under the age of 18, have the right to make medical decisions on their own behalf, such as minors who are married, widowed or divorced, minors who are parents, etc.);
- Mature minors—Michigan law recognizes that some minors may be sufficiently "mature" to give consent to medical treatment, even though they do not qualify as "emancipated"); or
- Certain minors seeking care for drug addiction, sexually transmitted diseases, emotional disorders, or abortion or mental health treatment.

Because Michigan law does not specifically address consent of children with majority status in relation to research, VARI IRB will review issues of consent related to enrollment of these children in research on a case-by-case basis.

NOTE: For research conducted in jurisdictions other than Michigan, the research must comply with the state laws regarding the legal age of consent in all relevant jurisdictions. VARI's General Counsel will be consulted with regard to the laws in other jurisdictions.

Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. In Michigan, a guardian of a minor has the powers and responsibilities of a parent, including the duty to take reasonable care of the minor's physical well-being and protect the minor's property; facilitate the minor's education and social or other activities; and authorize medical or other professional care, treatment, or advice. (MCL 700.5215)

NOTE: For research conducted in jurisdictions other than Michigan, the research must comply with the State laws regarding guardianship in all relevant jurisdictions. VARI's General Counsel will be consulted with regard to the laws in other jurisdictions.

Fetus means the product of conception from implantation until delivery.

Dead fetus means a fetus that does not exhibits heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, or pulsation of the umbilical cord.

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

Neonate means a newborn.

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

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

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

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

Surrogate Consent is consent obtained from a legally authorized representative (LAR) on behalf of a research subject who is determined to lack decision-making capacity.

8.2 Involvement of Vulnerable Populations

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

45 CFR 46 has additional subparts designed to provide extra protections for vulnerable populations which also have additional requirements for IRBs. These are:

- Subpart B - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
- Subpart C - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- Subpart D - Additional Protections for Children Involved as Subjects in Research

HHS-funded research that involves any of these populations must comply with the requirements of the relevant Subparts. Research funded by other federal agencies may or may not be covered by the Subparts. For example, FDA regulations include additional protections only for children as subjects in research.

When following DoD regulations, research involving pregnant women, prisoners, and children are subject to the DHHS Subparts B, C. and D.

- For purposes of applying Subpart B, the phrase “biomedical knowledge” shall be replaced with “generalizable knowledge.”
- The applicability of Subpart B is limited to research involving pregnant women as participants in research that is more than minimal risk and included interventions or invasive procedures to the woman or the fetus or involving fetuses or neonates as participants.
- Research involving prisoners cannot be reviewed by the expedited procedure.
- When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum.
- In addition to allowable categories of research on prisoners in Subpart C, epidemiological research is also allowable when:
- The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.
- The research presents no more than minimal risk.

The research presents no more than an inconvenience to the participant. VARI limits the application of the FWA to federally funded research. Consequently under VARI’s FWA the Subparts only apply to HHS-funded research and research funded by another federal agency that requires compliance with the Subparts (FDA regulations include Subpart D, which applies to all FDA-regulated research). The following policies and procedures, which are based on the Subparts, apply to all research regardless of funding. The individual sections describe how the Subparts apply to HHS-funded research.

8.3 Responsibilities

- The PI is responsible for identifying the potential for enrolling vulnerable subjects in the research proposal. The PI is responsible for identifying subjects who are at risk for impaired decision-making capacity, and who are being asked to participate in a research study with greater than minimal risk.
- The IRB shall include representation (members or ad hoc consultants) of individual(s) interested in or who have experience with vulnerable populations involved in the research proposal under review.
- The IRB reviews the PI’s justifications for including vulnerable populations in the research to assess appropriateness of the research proposal.

- The IRB must ensure that additional safeguards have been included in each study to protect the rights and welfare of vulnerable subjects, as needed, at the time of initial review of the research proposal.
- Information reviewed as part of the continuing review process should include the number of subjects considered to be members of specific vulnerable populations.
- The IRB should be knowledgeable about and experienced in working with populations who are vulnerable to coercion and undue influence. If the IRB requires additional qualification or expertise to review a protocol, it will obtain consultation.

8.4 Procedures

Initial Review of Research Proposal:

- The PI identifies the potential to enroll vulnerable subjects in the proposed research at initial review and provides the justification for their inclusion in the study.
- The IRB evaluates the proposed plan for consent of the specific vulnerable populations involved. If the research involves adults unable to consent, the IRB evaluates the proposed plan for obtaining permission from LARs.
- The IRB evaluates and approves the proposed plan for the assent of subjects, as applicable.
- The IRB evaluates the research to determine the need for additional protections and considers the use of a data and safety monitoring board or data monitoring committee, as appropriate.
- The PI provides appropriate safeguards to protect the subject's rights and welfare, which may include the addition of an independent monitor. The independent monitor is a qualified individual not involved in the research study who will determine the subject's capacity to provide voluntary informed consent.
- The IRB assess the adequacy of additional protections for vulnerable populations provided by the PI.

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

8.5 Research Involving Pregnant Women, Human Fetuses and Neonates

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

VARI does not currently, nor does it foresee engaging in research involving neonates. If VARI were to be presented with a research proposal involving neonates, VARI would develop appropriate policies and procedures to ensure protection of this population.

8.5.1 Research Involving Pregnant Women or Fetuses

8.5.1.1 Research Not Funded by HHS

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

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

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

8.5.1.2 Research Funded by HHS

For HHS-funded research, 45 CFR 46 Subpart B applies to all research involving pregnant women. Under 45 CFR 46 Subpart B, pregnant women or fetuses may be involved in research funded by HHS if all of the following conditions are met:

- Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risk to pregnant women and fetuses.
- The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
- Any risk is the least possible for achieving the objectives of the research;
- If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman or the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent.
- If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
- Each individual providing consent under paragraph 4 or 5. of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
- For children who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in *Section 9.7.2*;
- No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
- Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
- Individuals engaged in the research will have no part in determining the viability of a neonate.

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

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

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

8.6 Research Not Otherwise Approvable

8.6.1 Research Not Funded by HHS

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

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

8.7 Research Funded by HHS

HHS-funded research that falls in this category must be approved by the Secretary of Health and Human Services. If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and the research is not approvable under the above provisions, then the research will be sent to OHRP for HHS review.

8.8 Research Involving Prisoners

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

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

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

While VARI does not anticipate engaging in research involving prisoners, should such a study be submitted for IRB consideration or if a subject on a VARI protocol becomes incarcerated, we will follow the procedures outlined below.

8.8.1 Applicability

This policy applies to all biomedical and behavioral research conducted under the auspices of VARI involving prisoners as subjects. Even though the VARI IRB may approve a research protocol involving prisoners as subjects according to this policy, PIs are still subject to the Administrative Regulations of the Michigan Department of Corrections and any other applicable State or local law (45 CFR 46.301).

8.8.2 Minimal Risk

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

8.8.3 Composition of the IRB

In addition to satisfying the general requirements detailed in the IRB section of this manual, when reviewing research involving prisoners, the IRB must also meet the following requirements:

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

8.8.4 Review of Research Involving Prisoners

The prisoner representative must review research involving prisoners, focusing on the requirements in Subpart C.

The prisoner representative must receive all review materials pertaining to the research (same as primary reviewer)

The prisoner representative must be present at a convened meeting when the research involving prisoners is reviewed. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved. The prisoner representative may attend the meeting by phone, video-conference, or webinar, as long as the representative is able to participate in the meeting as if they were present in person at the meeting.

The prisoner representative must present his/her review either orally or in writing at the convened meeting of the IRB when the research involving prisoners is reviewed.

Modifications. Minor modifications to research may be reviewed using the expedited procedure. Modifications involving more than a minor change must be reviewed by the convened IRB using the same procedures for initial review, including review by the prisoner representative.

Continuing review. Continuing review must use the same procedures used for initial review, including review by the prisoner representative.

Expedited Review. If research involving prisoners is reviewed by expedited review, prisoner representation will be included in the review when possible.

8.8.5 Incarceration of Enrolled Subjects

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

- Confirm that the subject meets the definition of a prisoner;
- Terminate enrollment or review the research study under Subpart C if it is feasible for the subject to remain in the study;
- Before terminating the enrollment of the incarcerated subject, the IRB should consider the risks associated with terminating participation in the study. If the subject cannot be terminated for health or safety reasons, one of two options are available:
    - Keep the subject enrolled in the study and review the research under Subpart C. If some of the requirements of Subpart C cannot be met, but it is in the best interests of the subject to remain in the study, keep the subject enrolled and inform OHRP of the decision along with the justification;
    - Remove the subject from the study and keep the subject on the study intervention under an alternate mechanism such as compassionate use, off label use, etc;
    - If a subject is incarcerated temporarily while enrolled in a study:
    - If the temporary incarceration has no effect on the study, keep the subject enrolled; and
    - If the temporary incarceration has an effect on the study, handle according to the above guidance.

8.8.6 Additional Duties of the IRB

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

- The research falls into one of the following **permitted categories** (45 CFR 46.306):
    - Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

- Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
- Research on conditions particularly affecting prisoners as a class (for example, research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research;
- Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research.

- Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
- The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
- Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the PI provides to the IRB, justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
- The information is presented in language which is understandable to the subject population;
- Adequate assurance exists that parole Board will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
- Where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing subjects of this fact.

8.8.7 Certification to HHS

Under 45 CFR 46.305(c), the institution responsible for conducting research involving prisoners that is supported by HHS shall certify to the Secretary (through OHRP) that the IRB has made the seven findings required under 45 CFR 46.305(a). For all HHS conducted or supported

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

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

The term "research proposal" includes:

- The IRB-approved protocol; any relevant HHS grant application or proposal;
- Any IRB application forms required by the IRB; and
- Any other information requested or required by the IRB to be considered during initial IRB review.

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

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

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

8.8.8 Waiver for Epidemiology Research

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

8.9 Research Involving Children

The following applies to all research involving children, regardless of funding source. The requirements in this section are consistent with 45 CFR 46 Subpart D, which applies to HHS-

funded research and 21 CFR 50 Subpart D, which applies to FDA-regulated research involving children.

8.9.1 Allowable Categories

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

1. Research not involving greater than minimal risk. Provided that the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in *Section 8.9.2*.
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects Provided that the IRB finds and documents that:
   a. The risk is justified by the anticipated benefit to the subjects;
   b. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative options; and
   c. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in *Section 8.9.2*.
3. Research involving greater than minimal risk and no reasonable prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition. Provided that the IRB finds and documents that:
   a. The risk represents a minor increase over minimal risk;
   b. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
   c. The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
   d. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in *Section 8.9.2*.
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children.
   a. Federally-funded research in this category must be approved by the Secretary of Health and Human Services;
   b. FDA-regulated research in this category must be approved by the Commissioner of Food and Drugs.
   c. For non-federally-funded, non-FDA research, the IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on either:
      (1) That the research satisfies the conditions of the previous categories, as applicable; or

(2) The following:

- The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
- The research will be conducted in accord with sound ethical principles; and
- Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in *Section 8.9.2*.

8.9.2 Parental Permission and Assent

8.9.2.1 Parental Permission

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

Parents or guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary, as described in *Section 7.5*.

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

Permission from both parents is required for research to be conducted under Categories 3 & 4 above unless:

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

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

- The research meets the provisions for waiver in *Section 7.9*; or
- If the IRB determines that the research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), the IRB may waive the parental permission requirements provided that an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

Parental permission may only be waived for research covered by the FDA regulations if the criteria for an exception from the general requirements for informed consent under 21 CFR 50.23 or for emergency research under 21 CFR 50.24 are satisfied.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by *Section 1.6*.

8.9.2.2 Assent from Children

When children are to be enrolled in research, the IRB is obligated to determine that adequate provisions are made for soliciting the assent of children when, in the judgment of the IRB, the children are capable of providing assent. “Assent” is defined as a child’s affirmative agreement to participate in research. Mere failure on the part of a child to object, absent affirmative agreement to participate, should not be construed as providing assent.

In determining whether children are capable of providing assent, the IRB should take into consideration the ages, maturity, and psychological state of the children to be involved. The IRB has the discretion to judge children’s capacity to assent for all of the children to be involved in a proposed research activity, for some, or to make the determination on an individual basis.

Likewise, in evaluating the provisions for obtaining assent, the IRB should take into account the nature of the proposed research activities and the ages, maturity, and psychological state of the children to be involved. For research activities involving adolescents whose capacity to understand resembles that of adults, the assent procedure should include information similar to what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be. For example, what the experience will be, how long it will take, and whether it might involve any pain or discomfort. The assent procedure should incorporate provisions to ensure that the child is enabled to make a free choice about participation.

8.9.2.3 Waiver of Assent

The IRB may waive the requirement for assent of children if it determines and documents that:

1. The capability of an individual child, some, or all children to provide assent is so limited that they cannot reasonably be consulted;
2. The interventions or procedures involved in the research hold out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research; or
3. That even though the children are capable of providing assent:
    a. The research involves no more than minimal risk;
    b. The waiver will not adversely affect the rights and welfare of the subjects;
    c. The research could not practicably be carried out without the waiver; and
    d. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

8.9.2.4 Documentation of Assent

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

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

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

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

8.9.2.5 Disagreement between the Parent and Child

Parents and children will not always agree on whether the child should participate in research. Unless the requirement for child assent or parental permission has been waived by the IRB, both child assent and parental permission are necessary prerequisites for a child to participate in research. Objection by either the parent(s) or child must be respected and neither should be subjected to coercion or undue influence.

8.9.2.6 Children Who are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research involving greater than minimal risk and no prospect of direct benefit to individual

subjects, but likely to yield generalizable knowledge about the subject's disorder or condition (Categories 3 & 4 in *Section 8.7.1*), only if such research is:

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

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

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

8.10 Persons with Impaired Decision Making Capacity

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

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

- Only persons with impaired decision making capacity are suitable as research subjects. Competent persons are not suitable for the proposed research. The PI must demonstrate to the IRB that there is a compelling reason to include persons with impaired decision making capacity as subjects. 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 subject. 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 subject’s LAR is well informed regarding their roles and obligations to protect persons with impaired decision making capacity. LAR, or guardians, must be given descriptions of the proposed research studies and the obligations of the person’s LAR. The LAR must be informed that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the best interest of the potential research subject.

When following Department of Defense (DoD) regulations:

- If consent is to be obtained from the subjects’ LAR, the research must intend to benefit the individual participant.
- The determination that research is intended to be beneficial to the individual subject must be made by an IRB.

8.10.1 Determination of Decision-Making Capacity

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

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

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

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

For research protocols involving subjects who have fluctuating or limited decision making capacity, the IRB may ensure that PIs establish and maintain ongoing communication with involved caregivers. Periodic re-consent should be considered in some cases. Third-party consent monitors may be used during the recruitment and consenting process, or waiting periods may be required to allow more time for the potential subject to consider the information that has been presented. If in doubt, researchers should not seek participation from the subject.

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

Both PIs and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For subjects with fluctuating decision-making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consenter may be necessary.

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

In the event research subjects become impaired in decision-making capacity after enrollment, and this is not anticipated in the research plan, the PI is responsible for notifying the IRB of the situation. The PI is responsible for developing a monitoring plan which follows the guidelines outlined above.

8.10.2 IRB composition

The IRB membership must include representation via a member or consultant with expertise in issues of impaired decision-making capacity, e.g., a family member of such a person or a representative of an advocacy group for that population. If the IRB regularly reviews research that involves persons who with impaired decision-making capacity, consideration shall be given to the inclusion of one or more IRB members who are knowledgeable about and experienced in working with these subjects. When inclusion of subjects with impaired decision-making capacity has not been approved by the IRB and the PI wishes to enroll one or more subjects with impaired decision making capacity in an active protocol, the PI must seek IRB approval from the IRB prior to proceeding with the enrollment.

8.10.3 IRB Review

In reviewing research involving persons with impaired decision-making capacity, the IRB considers whether the following are required and appropriate:

- Whether subjects with diminished capacity can be included in the research, as the target of the research;
- The rationale for including subjects who do not have the ability to consent (e.g. risk/benefit relationship);
- The method used to assess the subject's consent capacity;
- The process for obtaining surrogate permission for subjects who do not have the ability to consent;
- The process to seek assent according to the capacity of the subject and to respect dissent;
- Additional safeguards to protect the rights and welfare of these subjects (e.g. third party observation of the consent/permission/assent process, consent modifications, more frequent continuing review, research subject advocate); and
- Situations which may involve fluctuating capacity (e.g. intermittent capacity, drug-related capacity), regaining capacity, or progressively diminishing capacity and re-consenting processes, when appropriate.

9 FDA Regulated Research

VARI is not a clinical facility, therefore, VARI IRB will not engage in review of emergency use of a test article, research involving Humanitarian Use Devices, expanded access and compassionate use trials, or planned emergency research studies. FDA regulations apply to any research that involves a *test article* in a *clinical investigation* involving *human subjects* as defined by FDA regulations. For FDA regulated research, the IRB must apply the FDA regulations at 21 CFR 50 and 21 CFR 56, as well as, 45 CFR 46, as appropriate.

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

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

9.1 Definitions

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

Dietary Supplement. A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains a dietary ingredient. The dietary ingredients in these products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. Dietary supplements can be found in many forms such as tablets, capsules, soft gels, liquids, or powders. See section 201(ff) of the FD&C Act (21 U.S.C. 321(ff)).

Investigational Device. Investigational device is a device, including a transitional device that is the object of an investigation. Investigation is a clinical investigation or research involving one or more subjects to determine the safety and/or effectiveness of a device.

Investigational Device Exemption (IDE) means an investigational device exemption in accordance with 21 CFR 812.

Investigational Drug. A drug, approved or unapproved, used in an experiment. An experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

Investigational New Drug (IND). An investigational drug for clinical research use is one for which the PI or a sponsor has filed an IND application (21 CFR 312) or an approved drug that is

being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.

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

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

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

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- 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.

Non-Significant Risk (NSR) Device is an investigational device that does not pose a significant risk.

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

Humanitarian Device Exemption (HDE) is an application that is similar to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of sections 514 and 515 of the Food, Drug, and Cosmetic Act (the Act). FDA approval of an HDE authorizes an applicant to market a Humanitarian Use Device (HUD), subject to certain profit and use restrictions set forth in section 520(m) of the Act. Specifically, as described below, HUDs cannot be sold for profit, except in narrow circumstances, and they can only be used in a facility after an IRB has approved their use in that facility, except in certain emergencies.

9.2 FDA Exemptions

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

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review (21 CFR 56.104(c)).
2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or

below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture (21 CFR 56.104(c)).

9.3 Procedures

At initial submission, the PI must indicate whether the research involves a test article and is a clinical investigation involving human subjects on the application form.

During the pre-review process, the IRB Compliance Specialist will confirm whether FDA regulations are applicable. If FDA regulations apply and the research is not exempt, the IRB Specialist will indicate on the IRB agenda that the protocol is an FDA-regulated study.

If required by the sponsor (see *Section 1.3*), the PI will indicate on the application form that ICH-GCP compliance is required and will affirm compliance. If the study involves investigational drugs and is industry sponsored and the PI has not indicated ICH-GCP compliance, the IRB Compliance Specialist will confirm with the Office of Grants and Contracts whether ICH-GCP compliance is required and obtain PI affirmation of compliance.

9.4 Investigator Responsibilities

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

- The PI is responsible for reading and understanding the information in the PI's brochure, including the potential risks and side effects of the drug or device.
- The PI is responsible ensuring that a clinical investigation is conducted according to the signed PI statement for clinical investigations of drugs, including biological products, or agreement for clinical investigations of medical devices, the investigational plan and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.
- The PI is responsible for personally conducting or supervising the investigation. When certain study-related tasks are delegated by a PI, the PI is responsible for providing adequate supervision to research staff to whom tasks are delegated.
- The PI must maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (e.g., can refer to an individual's CV on file), and identify the dates of involvement in the study. A PI should maintain separate lists for each study that he/she conducts.
- The PI is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.
- The PI is responsible for protecting the rights, safety, and welfare of subjects under his/her care during a clinical trial. This responsibility includes:

- Providing reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention,
- Providing reasonable access to needed medical care, either by the PI or by another identified, qualified individual (e.g., when the PI is unavailable, when specialized care is needed),
- The PI is responsible to maintain adequate and accurate records in accordance with FDA regulations and to make those records available for inspection by the FDA. These records include drug and device accountability, case histories, consent forms and documentation that consent was obtained prior to any participation in the study. Records must be maintained for a minimum of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such. Other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors may necessitate retention for a longer period of time.

- The PI shall furnish all reports, including reports of adverse events, to the sponsor of the drug who is responsible for collecting and evaluating the results obtained.
- The PI is responsible for controlling drugs, biological products, and devices according to FDA regulations and the Controlled Substances Act, as applicable.
- The PI proposing the drug/device research will be required to provide a plan, to be evaluated by the IRB that includes storage, security, and dispensing of the drug/ biologics/device.
- The PI is responsible for the investigational drug/device accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability.
- The PI may delegate the responsibility for drugs/biologics accountability to the Pharmacy Service at the external clinical site.
- All devices received for a study must be stored in a locked environment under secure control with limited access. The area must be within an area under the PI's control. Proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use, and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.
- The PI shall furnish all reports required by the sponsor of the research including progress reports, safety reports, final reports, and financial disclosure reports.
- The PI will permit inspection of research records by the sponsor, sponsor representatives, HRPP and IRB representatives, the FDA, accrediting bodies, and any other agencies or individuals entitled to inspect such records under organizational policy, contractual agreement, or regulation.

9.5 Dietary Supplements

Research involving dietary supplements may or may not fall under FDA regulations. Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, a dietary supplement is not

considered a drug and is not subject to the premarket approval requirements for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose). Whether a study falls under FDA oversight is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, FDA regulations do not apply. However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, FDA regulations do apply. Studies involving the ingestion of dietary supplements that are not subject to FDA oversight are considered research, and must be reviewed by the IRB.

Similarly, whether an IND is needed for a study evaluating a dietary supplement is determined by the intent of the study. If the study is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required. However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required under 21 CFR 312. For example, a study designed to study the relationship between a dietary supplement's effect on normal structure or function in humans (e.g., calcium and bone mass) or to characterize the mechanism by which a dietary supplement acts to maintain such structure or function (e.g., fiber and bowel regularity) would not need to be conducted under an IND. However, a study designed to evaluate a dietary supplement's ability to prevent osteoporosis or to treat diarrhea or constipation would need to be conducted under an IND.

9.5.1 Research Plan

As with the study of any investigational product, the researcher must supply the IRB with sufficient information to determine that the criteria for approval are satisfied and to determine or verify whether or not the research requires an IND. Applications should provide detail consistent with that expected on a drug protocol and consistent with the level of risk associated or anticipated with the research. At a minimum, the research plan should provide the following information regarding the supplement: Name, Manufacturer, Formulation, Dosage, Method/Route of Administration, Mechanism of Action, Known Drug Interactions, Risk Profile, IND number (or justification for why an IND is unnecessary), Documentation evidencing approval for use in humans, Documentation or certification of Quality or Purity. As with drugs and devices there should be an accountability plan for the product describing where the product will be stored and how it will be dispensed, usage tracked, and disposal or return. If the study entails greater than minimal risk, a plan for Data & Safety Monitoring must be included.

9.6 Investigational Drugs and Devices in Research

9.6.1 IND/IDE Requirements

For protocols evaluating the safety or effectiveness of medical devices or experiments utilizing drugs, biologics, dietary supplements, and other compounds that may be considered a drug under FDA regulations, the PI must indicate on the IRB application whether or not an IDE or IND is in place, and, if not, the basis for why an IDE or IND is not needed. Such documentation

is typically provided by the sponsor, or by the sponsor-investigator for investigator-initiated studies. Documentation of the IND/IDE could be a:

- Industry sponsored protocol with IND/IDE number indicated on the protocol;
- Letter from FDA;
- Letter from industry sponsor; or
- Other document and/or communication verifying the IND/IDE.

For investigational devices, the study may be exempt from IDE requirements or, in the case of Non-significant Risk (NSR) device studies, follow abbreviated IDE requirements which do not require formal approval by the FDA. If a sponsor has identified a device study as exempt or NSR, then the PI should include this documentation with the submission to the IRB justifying the basis for exempt or NSR categorization. If the FDA has determined that the study is exempt or NSR, documentation of that determination must be provided.

The convened IRB will review the application and, based upon the documentation provided, determine: (1) that there is an approved IND/IDE in place, (2) that the FDA has determined that an IND is not required or that a device study is exempt or NSR, or, (3) if neither of the above, whether or not an IND is necessary, or that a device study is exempt or NSR, using the criteria below. Depending on the determination made at the IRB meeting, subsequent verification of the existence of an IND or IDE and its status can be made by the Chair or Vice Chair or remanded back to the IRB for further review. Approval of the research cannot be granted until the IND/IDE status is determined, and, if necessary, an approved IND or IDE is in place.

9.6.1.1 IND Exemption

For drugs, an IND is not necessary if the research falls in one of the following categories:

- The drug being used in the research is lawfully marketed in the United States and all of the following requirements are met:
  - The research is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug
  - The research is not intended to support a significant change in the advertising for the product;
  - The research does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product
  - The research is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]
  - The research is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]
  - The research does not intend to invoke FDA regulations for planned emergency research [21 CFR 50.24].

- The research only involves one or more of the following: (a) Blood grouping serum, (b) Reagent red blood cells or (c) Anti-human globulin;
- For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and b) it is shipped in compliance with 21 CFR 312.160
- A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

9.6.1.2 Exempted IDE Investigations

For devices, an IDE is not necessary if:

- The research involves a device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time ;
- The research involves a device other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence;
- The research involves 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, and
  - Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;
- The research involves a device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;
- The research involves a device intended solely for veterinary use;
- The research involves a device shipped solely for research on/or with laboratory animals and labeled in accordance with 21 CFR 812.5(c);
- The research involves a custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

9.6.1.3 Significant and Non-significant Risk Device Studies

A device study is a Non-Significant Risk (NSR) Device study if it does not meet the definition of a Significant Risk (SR) Device study.

Under 21 CFR 812.3(m), an SR device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is purported or represented to be for use 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.

Determinations of SR versus NSR are made by the convened IRB. The IRB will document the determination of SR or NSR and the rationale for the determination in the meeting minutes. If the IRB determines a study to be SR, and an IDE is not in place, the sponsor or sponsor-PI should either consult with the FDA or provide additional information to the IRB for consideration. The study may not proceed until an IDE is in place or determined unnecessary (study is NSR or exempt).

10 Unanticipated Problems Involving Risks to Subjects or Others

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

The following procedures describe how UAPs involving risk to subjects or others are handled in research under the auspices of VARI. Unless specifically required by the IRB, the VARI IRB does not usually accept reports of adverse events that do not meet the definition of an UAP Involving Risks to Subjects or Others. Per federal regulation, Unanticipated Adverse Device Events (UADEs) must be reported to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the PI first learns of the event (21 CFR 812.150(a)(1)).

When following Department of Defense (DoD) regulations, any unanticipated problem involving risks to participants or others for any DoD-supported research must be promptly reported (within 30 days) to the DoD Human Research Protection Officer.

10.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UAPs). UAPs refer to any incident, experience, outcome, or new information that:

- Is unexpected;
- Is related or possibly related to participation in the research; and
- Indicates that subjects or others maybe at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unexpected. The incident, experience or outcome is not expected (in terms of nature, severity, or frequency) given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent documents; and the characteristics of the subject population being studied.

Related. There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

Adverse Event (AE). An AE is defined as any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article.

Unanticipated Adverse Device Effect (UADE). An UADE means any serious adverse effect on the health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

10.2 Procedures

10.2.1 Reporting

PIs must report possible UAPs and UADEs to the sponsor, if applicable, and the IRB as soon as possible, but in no event later than 10 working days after the PI first learns of the event.

PIs must promptly report the following problems to the IRB:

- AEs that appear to have caused direct harm to subjects that in the opinion of the PI may meet the criteria for a UAP involving risk to subjects or others.
- For FDA-regulated research of drugs or biologics, AEs that fall within any of the following criteria:
  - A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure.
  - A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population.
  - Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects.
  - An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations.
  - A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison).
  - Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects.
- IND Safety Reports from sponsors that meet the criteria for a UAP involving risk to subjects.
- Unanticipated adverse device effects (UADEs).
- An unanticipated event related to the research that appears to have exposed subjects to potential risk but that does not involve direct harm to subjects.
- An unanticipated event related to the research that may have exposed individuals other than the research subjects (e.g., PIs, research assistants, students, the public, etc.) to potential risk.

- New information that indicates an increase to the risks or decrease to potential benefits of the research. For example:
  - An interim analysis or safety monitoring report indicates that the frequency or magnitude of harms may be greater than initially presented to the IRB.
  - A paper is published from another study that shows that the potential benefits of the research may be less than initially presented to the IRB.
- A breach of confidentiality.
- Sponsor imposed suspension or termination due to potential increased risk.
- Any other event that indicates participant or others might be at risk of serious, unanticipated harms that may be reasonably related to the research.

10.2.2 Submission of Reports

PIs or the study team must report possible UAPs to the IRB Office in writing using the *Event Reporting Form (HRPP-FORM-005).* The written report should contain the following:

- Detailed information about the possible UAP, including relevant dates.
- Any corrective action, planned or already taken, to ensure that the possible UAP is corrected to minimize reoccurrence.
- An assessment of whether any subjects or others were placed at risk as a result of the event or suffered any physical, social, or psychological harm and any plan to address these consequences.
- If a report from a sponsor is the basis for the report, or a sponsor has requested the submission to the IRB, the report should be accompanied by an analysis from the sponsor detailing (1) how the event or problem satisfies the definition of a UAP, (2) proposed study-wide corrective actions or modifications to the research along with a timeline for anticipated completion of the actions, and (3) whether or not the problem has been reported as a UAP to any relevant federal agencies.
- Any other relevant information.
- Any other information requested by the IRB Office.

A report of a possible UAP involving risks to subjects or others will be immediately forwarded by the IRB Office staff to the HRPP Director, IRB Chair, or designee if the IRB Office staff believes that immediate intervention may be required to protect subjects or others from serious harm.

Upon receipt of a report of a possible UAP from someone other than the PI or study staff, the IRB Chair will notify the PI on the study when appropriate.

10.2.3 IRB Procedures for Handling Reports of Possible Unanticipated Problems

10.2.3.1 Review by IRB Staff and Chair

Upon receipt of an *Event Reporting Form (HRPP-FORM-005)*, the IRB Office staff will check the form for completeness. If any applicable sections of the form are incomplete or have not been answered satisfactorily, the IRB staff will contact the PI or the designated contact person to obtain additional information. Corrections are documented in the IRB file, indicating the date, the person spoken with, and the IRB staff making the correction.

The IRB Chair and/or other experienced member(s), designated by the IRB Chair, receives and reviews the report of the event(s) considered to be an UAP. The IRB Chair (or designee) will make the final determination as to whether the event is to be regarded as an unanticipated problem.

Based on the information received from the PI, the IRB Chair or designee may temporarily stop the research to ensure protection of the rights and welfare of subjects. Directives made by the IRB Chair or designee must be reported at a meeting of the convened IRB.

The IRB or the IRB Chair (or designee) has authority to require submission of more detailed contextual information from the PI, the sponsor, the study coordinating center, or Data Safety Monitoring Board/Data Monitoring Committee (DSMB/DMC) about any adverse event occurring in a research protocol as a condition of the continuation of the IRB's approval of the research.

If the reviewer considers that either (1) the problem was foreseen OR (2) no subject or others were harmed AND subjects or others are not at increased risk of harm, the reviewer indicates on the form that the problem is not a UAP. The form is filed in the protocol record, the determination is communicated to the PI and will be reported to the IRB at the next convened meeting.

If the reviewer considers that the problem is a UAP, but that the risk is no more than minimal, the IRB member will review:

- The approved protocol;
- The approved consent document;
- Previous reports of UAPs involving risks to subjects or others; and/or
- The Investigator's brochure, if one exists.

After reviewing all of the materials, the IRB reviewer will discuss with the IRB Chair appropriate actions depending on the nature of the risk involved, including requiring modification of the protocol or the consent form, as applicable. The results of the review will be recorded in the protocol file, communicated to the PI, and reported to the IRB. All events determined to be UAPs will be reported to the relevant regulatory agencies and institutional officials according to the procedures in *Section 14*.

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

10.2.3.2 IRB Review

When a UAP meets the criteria described above for referral to the convened IRB, the following procedures will be invoked.

The primary reviewer will be given the protocol file, the approved consent document, previous reports of UAPs involving risks to subjects or others, the Investigator's Brochure (if one exists), the event report, and recommendations from the IRB Chair or designee, when appropriate. All IRB members will receive the event report.

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

- Whether the reported event is a UAP involving risks to subjects or others according to the definition in this policy;
- What action in response to the report is appropriate;
- Whether suspension or termination of approval is warranted; and
- Whether further reporting to VARI and/or federal officials is required.
- If the IRB finds that the event is not a UAP involving risks to subjects or others, according to the definition in the policy, the IRB may recommend any of the following actions:
  - No action;
  - Require modifications to the protocol;
  - Revise the continuing review timetable;
  - Modify the consent process;
  - Modify the consent document;
  - Provide additional information to current subjects (e.g., whenever the information may relate to the subject's willingness to continue participation);
  - Provide additional information to past subjects;
  - Require additional training of the PI and/or study staff; and/or
  - Other actions appropriate for the local context.
- If the IRB finds that the event is a UAP involving risks to subjects or others, the IRB may recommend any of the following actions:
  - Require modifications to the protocol;
  - Revise the continuing review timetable;
  - Modify the consent process;
  - Modify the consent document;
  - Provide additional information to current subjects (e.g., whenever the information may relate to the participant's willingness to continue participation);
  - Provide additional information to past subjects;
  - Require additional training of the PI and/or study staff;
  - Require that current subjects re-consent to participation;

- Monitor of the research;
- Monitor of the consent process;
- Make a referral to other organizational entities (e.g., General Counsel, IO);
- Suspend the research;
- Terminate the research; and/or
- Other actions appropriate for the local context.

- If a report suggests that subject safety is at risk, the IRB may immediately suspend or terminate the research. Any suspension or termination of research by the IRB must be promptly reported in writing to the IO, and any applicable regulatory agencies.
- If, after reviewing a report, the IRB finds that the event is a UAP involving risks to subjects or others or that suspension or termination of approval is warranted, the IRB will:
  - Notify the PI in writing of its findings, with copies to the PI's supervisor and/or Department Chair.
  - Report its findings and recommendations to the IO and General Counsel for further reporting as necessary.

11 Protocol Exceptions or Deviations

It is the policy of VARI IRB to be notified of any protocol deviations or exceptions. The following procedures describe how protocol exceptions and deviations are reported to the IRB.

11.1 Definitions

Exceptions. Protocol exceptions are defined as circumstances in which the specific procedures outlined in a protocol are not in the best interests of a specific patient/subject (example: patient/subject is allergic to one of the medications provided as supportive care). Usually this is considered a protocol deviation that is anticipated and occurs with prior approval from the sponsor and the IRB.

Deviations. A protocol deviation is defined as a violation that is unanticipated and happens without any prior approval by the sponsor and the IRB. Examples of a protocol deviation include, study visit scheduled outside protocol window, blood work drawn outside protocol window, etc. The IRB will review these reports for frequency and may audit any protocol reporting frequent deviations.

11.2 Exceptions

Exceptions are planned changes that the PI obtains approval from the sponsor and the IRB prior to implementation, using the *Protocol Modification Checklist (HRPP-CHK-003)*. Depending on the nature of the exception, an expedited review may be possible. In order to be approved by the IRB, exceptions must not increase risk or decrease benefit, affect the subject's rights, safety, welfare, or the integrity of the resultant data.

The only time a protocol exception would not require prior sponsor or IRB approval is when the exception is made to avoid an immediate hazard to the subject. The *Event Reporting Form (HRPP-FORM-005)* should be used to report the incident for IRB review.

11.3 Deviations

All deviations:

- Must be reported to the IRB Office using the *Event Reporting Form (HRPP-FORM-005).*
- Are reviewed to determine if they:
  - Are minor, and don't impact subject safety. These are acknowledged by the IRB Chair or designee.
  - Constitute non-compliance. In these cases, the deviations would be reviewed by a fully convened IRB for determination of non-serious, serious, or continuing non-compliance; the latter two must be reported to federal agencies and sponsors, as applicable.
  - Constitute unanticipated problems involving risks to subjects or others (UAP). In these cases, the deviations are reviewed at a fully convened meeting of the IRB for

confirmation of UAP status. If confirmed, this must be reported to federal agencies and sponsors, as applicable (*See Section 14*).

When a sponsor requests that the IRB be notified of a deviation, the completed form will be forwarded to the IRB chair or designate for review of the *Event Reporting Form (HRPP-FORM-005)* submitted by the PI.

Repetitive deviations may be ruled by the IRB to constitute non-compliance which may result in suspension of IRB approval. If the study is suspended by the IRB, this must be reported to federal agencies and sponsors, as applicable (*See Section 14*).

11.4 Reporting & Review

Event Reporting Forms (HRPP-FORM-005) are to be completed for those events that qualify as a protocol deviation or exception. These reports should be filed with the IRB Office. The IRB Office will forward the report to the IRB Chair or designee for review. The Chair may choose to place any deviation or exception on the agenda of the next convened IRB meeting for discussion. The PI may be asked to appear at that meeting to answer any questions or clarify issues for the IRB.

12 Non-compliance

As part of its commitment to protecting the rights and welfare of human subjects in research, VARI IRB reviews all reports and allegations of non-compliance and takes any necessary action to ensure the ethical conduct of research. (Also see Section 4.5 *PI Compliance Review* and Section 5 *Study Suspension, Termination and Investigator Hold*.)

All PIs and other study personnel involved in human subjects research are required to comply with all laws, regulations, and policies governing their research activities, as well as with requirements and determinations of the IRB.

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

12.1 Definitions

Non-compliance. Non-compliance is defined as failure to comply with any of the regulations and policies described in this document and failure to adhere to the determinations of the IRB. Non-compliance may be minor, sporadic, continuing, or serious.

Serious non-compliance. Serious non-compliance is defined as failure to follow any of the regulations and policies described in this document or failure to adhere to the determinations of the IRB and which, in the judgment of either the IRB Chair or the convened IRB, increases risks to subjects, decreases potential benefits, or compromises the integrity of the research and the institution.

Continuing non-compliance. Continuing non-compliance is defined as a pattern of non-compliance that, in the judgment of the IRB Chair or convened IRB, suggests a likelihood that instances of non-compliance will continue without appropriate intervention.

Allegation of Non-Compliance. Allegation of non-compliance is defined as an unproved assertion of non-compliance.

Finding of Non-Compliance. Finding of non-compliance is defined as an allegation of non-compliance that is proven true or a report of non-compliance that is clearly true. For example, a finding on an audit of an unsigned consent document, or an admission of a PI that the protocol was willfully not followed, would represent reports of non-compliance. In these instances, no further action is required to determine their truth and would therefore represent findings of non-compliance. Once a finding of non-compliance is proven, it must be categorized as serious, non-serious, or continuing.

12.2 Reporting

PIs and their study staff are required to report instances of possible non-compliance. The PI is responsible for reporting any possible non-compliance by study personnel to the IRB. Reports to the IRB that are not serious or continuing are typically protocol deviations. However, any individual or employee may report observed or apparent instances of non-compliance to VARI IRB. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality, and cooperating with any IRB and/or institutional review of these reports.

If an individual, whether PI, study staff or other person, is uncertain whether there is cause to report non-compliance, he or she may contact the HRPP Director or IRB Chair directly to discuss the situation informally via email or phone.

The PI should submit reports of non-compliance to the IRB Office within 10 working days of discovery of the non-compliance. The report must include a complete description of the non-compliance including any personnel involved.

Complainants may make reports via email or phone to the HRPP Director, IRB Chair or through Ethics Point at https://secure.ethicspoint.com/domain/media/en/gui/25544/index.html. Ethics Point is an external reporting service that provides a confidential method to bring concerns to the attention of management. All reports submitted through EthicsPoint are handled as promptly and discreetly as possible by staff at EthicsPoint, who will make the facts available only to those at VARI who need to know to investigate and resolve the matter, and will protect the complainant's identity unless the complainant chooses not to remain anonymous. Any HRPP problems or complaints reported via EthicsPoint will be reviewed in accordance with VARI procedures.

12.2.1 Review of Allegations of Non-compliance

All allegations of non-compliance will be re viewed by the IRB Chair and HRPP Director, who may request additional information or an audit of the research in question.

When the IRB Chair and the HRPP Director make a determination that non-compliance did not occur because the incident was within the limits of an approved protocol for the research involved, this determination is reported to the IRB and in writing to the PI, and, if applicable, to the reporting party. The determination letter will be copied to the IO, in cases where the IO and any other parties had been notified at the outset.

If in the judgment of the IRB Chair and the HRPP Director, the report or allegation represents non-compliance, the non-compliance will be processed according to *Section 12.2.2* Review of Findings of Non-compliance.

If in the judgment of the IRB Chair and HRPP Director, and in consultation with the IO (as appropriate), any allegation or findings of non-compliance that warrants suspension of the research before completion of the review or investigation, and in order to ensure protection of the rights and welfare of subjects, the IRB Chair may suspend the research as described in *Section 5* with subsequent review by the IRB.

The IRB Chair and HRPP Director may determine that additional expertise or assistance is required to make these determinations and may request that the IRB EC meet to discuss the allegations and to assist with the review and fact finding process. When the IRB EC assists in the review process, the IRB Chair is responsible for assuring that minutes of the meeting are generated to help support any determinations or findings made by the IRB EC.

12.2.2 Review of Findings of Non-compliance

Non-compliance is not serious or continuing:

When the IRB Chair and the HRPP Director determines that the non-compliance occurred, but the non-compliance does not meet definition of serious or continuing non-compliance, the determination is reported to the IRB and in writing to the PI and, if applicable, the reporting party. The IRB Chair and HRPP Director will work with the PI to develop a corrective action plan to prevent future non-compliance. The report of non-compliance and corrective action is reported to the IRB at their next convened meeting and a vote is taken on the proposed corrective action plan. If, however, the PI refuses to cooperate with the corrective action plan, the matter will be referred to the IO.

Serious or Continuing Non-compliance.

When the IRB Chair and HRPP Director determines that non-compliance has occurred and that the non-compliance may meet the definition of serious or continuing non-compliance, the report of non-compliance is referred for review by the IRB at the next convened meeting. The IRB Chair, in consultation with the HRPP Director, may decide to call an emergency IRB meeting should the circumstances warrant.

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

At this stage, the IRB may:

- Find that there is no issue of non-compliance;
- Find that there is non-compliance that is neither serious nor continuing and an adequate corrective action plan has been, or will be, put in place;
- Find that there is serious or continuing non-compliance and require corrective actions or approve or revise a proposed corrective action plan;
- Find that there may be serious or continuing non-compliance and direct that a formal inquiry (described in *Section 12.2.3*) be held; and
- Request additional information.

12.2.3 Inquiry Procedures

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

- Subjects' complaint(s) that rights were violated;
- Report(s) that the PI is not following the protocol as approved by the IRB;
- Unusual and/or unexplained adverse events in a study;
- Repeated failure of the PI to report required information to the IRB;
- Dissent among IRB members about whether the non-compliance is serious and/or continuing.

A recommendation may be made that the IO appoint a subcommittee consisting of IRB members, and non-members, if appropriate, to ensure fairness and necessary expertise. The subcommittee is given a charge by the IRB, which can include any or all of the following:

- Review the protocol(s) in question;
- Review any audit report(s) of the PI, if available;
- Review any relevant documentation, including consent documents, case report forms, subject's investigational and/or medical files etc., as they relate to the PI's execution of her/his study;
- Interview appropriate personnel if necessary;
- Preparation of either a written report of the findings, which is presented to the IRB at its next convened meeting;
- Recommend actions, if appropriate.

12.2.4 Final Review

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

- Request a corrective action plan from the PI;
- Verify that research subject selection is appropriate
- Require an observation of the actual informed consent process;
- Increase in data and safety monitoring of the research activity;
- Request a directed audit of targeted areas of concern;
- Request a status report after each subject receives intervention;
- Modify the continuing review cycle;
- Request additional PI and staff education;
- Notify current subjects, if the information about the non-compliance might affect their willingness to continue participation;
- Require modification of the protocol;
- Require modification of the information disclosed during the informed consent process;
- Require current subjects to re-consent to participation;
- Suspend the study (See below); or
- Terminate the study (See below).

In cases where the IRB determines that the event of non-compliance also meets the definition of a UAP involving risks to subjects or others, the policy and procedure for review of such events will also be followed (See *Section 10*).

The PI is informed of the IRB determination and the basis for the determination in writing and is given an opportunity to respond. If the IRB determines that the non-compliance was serious or continuing, the results of the final review will be reported as described below in *Section 14*.

12.3 IRB Non-Compliance

When a complaint, concern, QA finding, or other report or issue indicates that the IRB may be in serious or continuing non-compliance, the IO will review the issue, and when merited, convene others (e.g., General Counsel, Chief Scientific Officer, Director of Compliance) to investigate the allegation and provide a report summarizing the findings, an analysis of whether the findings represent serious or continuing non-compliance, and, when appropriate, recommendations for corrective and preventative actions for the IO's consideration. The IO will review the report, determine whether serious or continuing non-compliance has occurred, determine corrective and preventative actions, when appropriate, and initiate any mandated or required reporting to federal agencies, sponsors, and others.

13 Complaints

The HRPP Director, IRB Chair, or designee will promptly handle (or delegate staff to handle), and, if necessary, investigate all complaints, concerns, and appeals received by the IRB Office. This includes complaints, concerns, and appeals from PIs, research subjects and others.

All complaints, written or verbal (including telephone complaints), regardless of point of origin, are recorded on a *Research Subject Inquiry/Complaint Form (HRPP-FORM-006)* and forwarded to the HRPP Director, IRB Chair, or designee.

If not anonymous, within 5 business days of receipt of the complaint, the HRPP Director or IRB Chair will generate an acknowledgement letter to the complainant that the complaint has been received and is being investigated. If the complainant's contact information has been provided, this will be handled confidentially. The identity of the complainant will not be revealed unless the complainant agrees that this information can be made known.

Upon receipt of the complaint, the HRPP Director or IRB Chair will make a preliminary assessment whether the complaint warrants immediate suspension of the research study. If a suspension is warranted, the procedures in *Section 5* will be followed.

If the complaint meets the definition of non-compliance, it will be considered an allegation of non-compliance according to *Section 13*.

If the complaint meets the definition of an unanticipated problem involving risk to subjects or others, it will be handled according to *Section 11*.

If the investigation of the complaint shows that there were no issues of non-compliance or UAP, the complainant will be contacted and notified.

14 Reporting to Regulatory Agencies and Institutional Officials

Federal regulations require prompt reporting to appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing non-compliance with the applicable regulations or, the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval. When following the Department of Defense (DoD) regulations, any suspension or termination of DoD-supported research must be promptly reported (within 30 days) to the DoD Human Research Protection Officer. VARI IRB complies with this requirement as follows.

14.1 Procedures

IRB staff will initiate the procedures outlined in *Section 14.1.1* as a result of the following, the IRB:

- Determines that an event may be considered an unanticipated problem involving risks to subjects or others;
- Determines that non-compliance was serious or continuing; or
- Suspends or terminates approval of research.

14.1.1 IRB Office Procedures

The HRPP Director or designee is responsible for preparing reports or letters which includes the following information:

- As applicable, the Federal-wide assurance (FWA) number and IRB registration.
- The nature of the event (unanticipated problem involving risks to subjects or others, serious or continuing non-compliance, suspension or termination of approval of research);
- Name of the institution conducting the research;
- Title of the research project and/or grant proposal in which the problem occurred;
- Name of the PI on the protocol;
- Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant(s), contract(s), or cooperative agreement(s));
- A detailed description of the problem including the findings of the organization and the reasons for the IRB's decision;
- Actions VARI is taking or implementation plans to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.);
- Plans, if any, to submit a follow-up or final report by:
    - A specific date;

- When an investigation/fact finding has been completed and/or a corrective action plan has been implemented;

Following the preparation of the draft report/letter, the following will take place:

- At a fully convened meeting, the IRB reviews the report/letter and the accompanying report documents, provides feedback on the adequacy of the materials.
- The IRB Chair, HRPP Director, General Counsel and the IO review the letter and report for appropriateness.
- The IO is the signatory for reports made to regulatory agencies.
- The HRPP Director or designee is responsible for assuring that the final report is sent to the appropriate federal agencies as follows:
  - OHRP, if the study is subject to HHS regulations or subject to a HHS federalwide assurance, and,
  - FDA, if the study is subject to FDA regulations.
  - If the study is conducted or funded by any Federal Agency other than HHS that is subject to "The Common Rule", the report is sent to OHRP or the head of the agency as required by the federal agency
  - Reporting to a regulatory agency is not required if the event occurred at a site that was not subject to the direct oversight by VARI, and the regulatory agency has been notified of the event by another party.
- The HRPP Director or designee is also responsible for providing copies of the final report to the following:
  - IRB, as part of the next agenda packet as an informational item
  - IO
  - PI
  - Sponsor, if the study is sponsored
  - Chair or supervisor of the PI
  - The Privacy Officer of a covered entity, if the event involved unauthorized use, loss, or disclosure of individually-identifiable patient information from that covered entity
  - The Information Security Officer of an organization if the event involved violations of information security requirements of that organization
  - Office of Risk Management, if appropriate
  - Others as deemed appropriate by the IO, HRPP Director, or CLO.

The HRPP Director ensures that all steps of this policy are completed within 30 working days of the determination or as agreed upon by the external agencies, e.g., OHRP, FDA, etc. For more serious actions, and as appropriate, the HRPP Director will expedite reporting.

15 Investigator Responsibilities

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

The following procedures describe PI responsibilities in the conduct of research involving human subjects.

15.1 Investigators

15.1.1 Principal Investigator (PI)

Individuals who can serve as PI or co-principal investigator (Co-PI) on Institution-based grants, contracts or cooperative agreements are full-time employees of VAI, VARI, VAEI or VAIGS, or are individual scientists who hold a fully-executed VARI-based joint faculty appointment. Eligibility to act as a PI or Co-PI on externally sponsored projects is granted by the Research Director, the VAEI Director, or the Dean of the Graduate School. To further clarify, the Institution provides the following information:

- Those authorized to submit grant or contract-based proposals or cooperative agreements for external funding as PI or Co-PI include VARI employees who hold the rank of Research Assistant Professor, Assistant Professor, Associate Professor, or Professor, and VAEI employees who hold the rank of Director, Associate Director, Dean, Associate Dean, Assistant Dean, Science Education Specialist, Evaluation Specialist, or Curriculum Specialist.
- Postdoctoral Fellows are permitted to submit fellowship-based applications with the approval of their supervisor.
- VAIGS graduate students in good standing may submit student-based applications with the approval of their academic supervisor and the Dean of the Graduate School.
- Submission of applications by jointly appointed faculty is subject to the terms and conditions of individual appointment agreements and the operational protocol established between their home institution and the VAI Office of Sponsored Research representing VAI, VARI, VAEI, or VAIGS as applicable.

The IRB recognizes one PI for each study. The PI has ultimate responsibility for the research activities.

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

15.1.2 Investigators

For the purposes of the HHS regulations, OHRP interprets an “investigator” to be any individual who is involved in conducting human subjects research studies. Such involvement would include:

- Obtaining information about living individuals by intervening or interacting with them for research purposes;
- Obtaining identifiable private information about living individuals for research purposes;
- Obtaining the voluntary informed consent of individuals to be subjects in research; and
- Studying, interpreting, or analyzing identifiable private information or data for research purposes.

For FDA regulated research, investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug or device is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the PI is the responsible team leader. "Sub-investigator" includes any other individual member of that team.

15.1.3 Research Team

The research team includes the PI and other individuals who contribute to the scientific development or execution of a project in a substantive, measurable way, whether or not they receive salaries or compensation under the protocol. The research team also consists of individuals who intervene or interact directly with human subjects for the express purposes of the research, or who analyze data and/or tissue derived from humans for the purposes of the research.

15.2 Responsibilities

In order to satisfy the requirements of this policy, PIs who conduct research involving human subjects must:

- Develop and conduct research that is in accordance with the ethical principles in the Belmont Report;
- Develop a research plan that is scientifically sound and minimizes risk to the subjects;
- Incorporate into the research plan, a plan to ensure the just, fair, and equitable recruitment and selection of subjects;
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, include additional safeguards in the study to protect the rights and welfare of these subjects;
- Ensure that the research plan includes adequate provisions for the monitoring of subjects and data to ensure the safety of subjects;
- Ensure that there are adequate provisions to protect the privacy interests of subjects;
- Ensure that there are adequate provisions to protect the confidentiality interests of subjects, including an information security plan that considers the collection, storage, maintenance, analysis, and transmission of data and other identifiable information;

- Have sufficient resources necessary to protect human subjects, including:
  - Access to a population that would allow recruitment of the required number of subjects.
  - Sufficient time to conduct and complete the research.
  - Adequate numbers of qualified staff.
  - Adequate facilities.
  - Necessary equipment.
  - A plan to ensure proper supervision of the research including a plan for periods of absence or decreased availability.
  - Availability of medical, psychological, or other support that subjects might require during or as a consequence of their participation in the research.
- Assure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise qualified to perform such under the applicable laws of Michigan and the policies of VARI;
- Assure that all study personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based;
- Assure that all persons assisting with the research are adequately trained and informed about the protocol and their specific duties and functions.
- Promptly report to the IRB for evaluation and approval any changes in, additions to, or loss of investigators or research staff;
- Protect the rights, safety, and welfare of research subjects;
- Ensure that when protected health information is used that legally effective HIPAA authorization is obtained for each subject unless the Privacy Board or IRB has approved a waiver of the authorization. This requirement does not apply when VARI research is not conducted under the auspices of a covered entity;
- Ensure that the language in the consent form is consistent with that in the protocol and, when applicable, in the HIPAA authorization;
- Obtain and document informed consent and ensure that no human subject is involved in the research prior to obtaining their consent or consent/permission from their legally authorized representative, unless a waiver of consent has been approved by the IRB;
- Have a procedure to receive questions, complaints, or requests for additional information from subjects and respond appropriately;
- Ensure that all information provided to the IRB is accurate and complete so that the IRB may fulfill its responsibilities to review the research and make the required determinations;
- Ensure that all research involving human subjects receives IRB approval in writing or a determination of exemption before commencement of the research;

- Ensure that all research involving human subjects is reviewed by other experts and organizational components and other regulatory committees as applicable to the research;
- Comply with all IRB decisions, conditions, and requirements;
- Ensure that protocols receive timely continuing IRB review and approval;
- Report unanticipated problems, deviations, complaints, non-compliance, suspensions, terminations, and any other reportable events to the IRB;
- Notify the IRB if information becomes available that suggests a change to the potential risks or benefits of the research;
- Obtain IRB approval before changes are made to the research unless a change is necessary eliminate apparent immediate hazards to the subject(s);
- Seek HRPP or IRB assistance when in doubt about whether proposed research requires IRB review;
- Retain records for the time period and in the manner required by applicable regulations, contractual agreements, and organizational policies.
- Additional investigator responsibilities when engaged in FDA-regulated research are described elsewhere in this document.

15.3 Training/Ongoing Education of Investigators and Research Team

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

15.3.1 Initial Education

PIs, key personnel, and other members of the research team must complete VARI Required Core Modules in CITI in the Protection of Human Research Subjects including the module on Conflicts of Interest. Evidence of current training (date of completion within 3 years of application date) for each member of the research team must be included in every new protocol application and application for continuing review.

Research protocols and applications for continuing review will be accepted and reviewed if the PI holds current certification of training, but prohibit the participation of individuals named on the protocol who have not completed the mandatory human subjects training.

New research protocols and applications for continuing review, may be approved by the IRB, but cannot accrue new subjects unless the PI has completed the initial or refresher training requirement.

Waiver of Initial Education

If individuals can provide documentation verifying that they have successfully completed human subjects research training during the past two years that is equivalent to that required by VARI, the individual may request a waiver of the requirement for Initial Education. However, all PIs or members of their research team must complete the requirements of Continuing Education at least triennially.

Education on Department of Defense Requirements

In addition to the Common Rule, human subjects research supported by the DoD is subject to requirements and ethical standards outlined in the Department of Defense Instruction 3216.02. Support of a study generally means the provision of funding, personnel (both military and civilian DoD employees), facilities, and any other resource.

IRB staff, Chair and members as well as PIs, key personnel, and other members of the research team become aware of specific requirements contained in the DoD regulations by reviewing the information in the Department of Defense Instruction 3216.02 and *the DoD IRB Reviewer Checklist* HRPP-CHK-020.01. The DoD IRB Reviewer Checklist is used to assess the protocol by the IRB.

15.3.2 Continuing Education and Recertification

PIs, key personnel, and other members of the research team must meet VARI continuing education requirement every three (3) years after certification of Initial Education for as long as they are involved in human subject research. There is no exception to this requirement. Acceptable training includes attendance at approved PRIM&R, OHRP, or FDA web-based training site. Other training may be acceptable. In these cases the researcher should check with the IRB Office for a determination. If other training is found to be acceptable, the individuals must provide certificates of completion. New research protocols and applications for continuing review, may be approved by the IRB, but cannot accrue new subjects unless the PI has completed the initial or refresher training requirement.

PIs who are also IRB Chair, IRB members, or IRB Office staff will satisfy the training requirements for IRB members and staff described under *Section 2.11*.

15.4 Investigator Concerns

PIs who have concerns or suggestions regarding VARI's HRPP or IRB(s) should convey them to the IO or other responsible parties (e.g. Director of Research/ Chief Scientific Officer, or Department Chair), when appropriate. The IO will review the issue, and when deemed necessary, convene the individuals involved to form a response to the PI or make necessary procedural or policy modifications, as warranted. In addition, the IRB Chair or the HRPP Director will be available to address PIs' questions, concerns and suggestions. Information regarding the concern will be shared with the IRB as appropriate. The IRB has final authority on protocol specific decisions.

16 Health Insurance Portability and Accountability Act (HIPAA)

The *Health Insurance Portability and Accountability Act of 1996* (HIPAA) required the creation of a Privacy Rule for identifiable health information. The resulting Privacy Rule, finalized in August 2002, set a compliance date of April 14, 2003. While the primary impact of the Privacy Rule is on the routine provision of health care and billing, the Rule also affects the conduct and oversight of research.

The Privacy Rule defines individually identifiable health information (IIHI) transmitted or maintained by a covered entity in any form (electronic, written or oral) as "protected health information" (PHI) and establishes the conditions under which investigators may access and use this information in the conduct of research.

VARI, while not a covered entity itself, does receive PHI from covered entities for research and is committed to the protection of this information in accordance with the provisions described in the applicable authorization, waiver or alteration of authorization, and/or any applicable agreements (i.e., data use agreement, business associate agreement). As an appropriately constituted IRB, VARI IRB has the authority to consider, and act upon, requests for a partial or complete waiver or alteration of the Privacy Rule's Authorization requirement for uses and disclosures of PHI for research. Under the Privacy Rule, an Authorization may be combined with the consent document for research. When a VARI researcher is leading or otherwise participating in collaborative research involving the authorized use of PHI, and the proposed consent document is combined with an Authorization, VARI IRB will conduct review of the research and the Authorization language to verify the presence of all required elements and statements.

16.1 Definitions (per HIPAA Privacy Booklet for Research)

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

Authorization. An individual's written permission to allow a covered entity to use or disclose specified PHI for a particular purpose. Except as otherwise permitted by the Rule, a covered entity may not use or disclose PHI for research purposes without a valid Authorization.

Covered Entity. A health plan, a health care clearinghouse, or a health care provider who transmits health information in electronic form in connection with a transaction for which HHS has adopted a standard.

Data Use Agreement. An agreement into which the covered entity enters with the intended recipient of a limited data set (LDS) that establishes the ways in which the information in the LDS may be used and how it will be protected.

Designated Record Set. A group of records maintained by or for a covered entity that includes (1) medical and billing records about individuals maintained by or for a covered health care provider; (2) enrollment, payment, claims adjudication, and case or medical management record systems maintained by or for a health plan; or (3) used, in whole or in part, by or for the covered entity to make decisions about individuals. A record is any item, collection, or grouping of

information that includes PHI and is maintained, collected, used, or disseminated by or for a covered entity.

Disclosure. The release, transfer, access to, or divulging of information in any other manner outside the entity holding the information.

Health Information. Health Information means any information, whether oral or recorded in any form or medium, that (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.

Health Insurance Portability and Accountability Act of 1996 (HIPAA, The Privacy Rule). This Act requires, among other things, under the Administrative Simplification subtitle, the adoption of standards, including standards for protecting the privacy of individually identifiable health information.

Individually Identifiable Health Information. Information that is a subset of health information, including demographic information collected from an individual, and (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; and (a) that identifies the individual; or (b) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

Limited Data Set (LDS). Refers to PHI that excludes 16 categories of direct identifiers and may be used or disclosed, for purposes of research, public health, or health care operations, without obtaining either an individual's Authorization or a waiver or an alteration of Authorization for its use and disclosure, with a data use agreement.

Minimum Necessary. The least information reasonably necessary to accomplish the intended purpose of the use, disclosure, or request. Unless an exception applies, this standard applies to a covered entity when using or disclosing PHI or when requesting PHI from another covered entity. A covered entity that is using or disclosing PHI for research without Authorization must make reasonable efforts to limit PHI to the minimum necessary. A covered entity may rely, if reasonable under the circumstances, on documentation of IRB or Privacy Board approval or other appropriate representations and documentation under section 164.512(i) as establishing that the request for protected health information for the research meets the minimum necessary requirements.

Protected Health Information (PHI). PHI is individually identifiable health information transmitted by electronic media, maintained in electronic media, or transmitted or maintained in any other form or medium. PHI excludes individually identifiable health information in education records covered by the Family Educational Rights and Privacy Act, as amended, 20 U.S.C. 1232g, records described at 20 U.S.C. 1232g(a)(4)(B)(iv), and employment records held by a covered entity in its role as employer.

Research. A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. This includes the development of research repositories and databases for research.

Use. With respect to individually identifiable health information, the sharing, employment, application, utilization, examination, or analysis of such information within the entity or health care component (for hybrid entities) that maintains such information.

Waiver or Alteration of Authorization. The documentation that the covered entity obtains from a researcher or an IRB or a Privacy Board that states that the IRB or Privacy Board has waived or altered the Privacy Rule's requirement that an individual must authorize a covered entity to use or disclose the individual's PHI for research purposes.

Workforce. Employees, volunteers, trainees, and other persons whose conduct, in the performance of work for a covered entity, is under the direct control of the covered entity, whether or not they are paid by the covered entity.

16.2 The IRBs Role under the Privacy Rule

Under the Privacy Rule, IRBs gained authority to consider, and act upon requests for a partial or complete waiver or alteration of the Privacy Rule's Authorization requirement for uses and disclosures of PHI for research.

The Privacy Rule does not change the composition of the VARI IRB. The Privacy Rule permits a covered entity to accept documentation of a waiver or alteration of Authorization from any qualified IRB or Privacy Board.

When acting upon a request to waive or alter the Authorization requirement, an IRB must follow the procedural requirements of the HHS Protection of Human Subjects Regulations (45 CFR 46) and/or, if applicable, FDA regulations, including using either the normal review procedures (review by the convened IRB) or the expedited review process.

When a request for a waiver or an alteration of the Authorization is considered by the convened IRB, a majority of the IRB members must be present at the meeting, including at least one member whose primary concerns are in nonscientific areas. In order for an approval of a waiver or an alteration of Authorization to be effective, it must be approved by a majority of the IRB members present at the convened meeting. HHS and FDA have established categories of research that may be reviewed by an IRB through an expedited review process. Expedited review of a request for a waiver or an alteration of the Authorization requirement is permitted where the research activity is on the HHS or FDA list of approved expedited categories and involves no more than minimal risk. In addition, 45 CFR 46.110 and 21 CFR 56.110 permit an IRB to use an expedited review process to review minor changes in previously approved research. For example, a modification to a previously approved research project, which only involves the addition of an Authorization for the use or disclosure of PHI to the IRB-approved informed consent, may be reviewed by the IRB through an expedited review process. If expedited review procedures are appropriate for acting on the request, the review may be carried out by the IRB Chair or designated IRB member reviewer (See *Section 3.4*). Regardless of the type of review, a member of the IRB who has a conflicting interest with respect to the PHI

use and disclosure for which a waiver or an alteration of Authorization is being sought, may not participate in the review.

VARI will not release PHI to researchers without individual authorization or proper documentation of an IRB or Privacy Board approval of a waiver or alteration of the requirement.

Waivers or alterations approved by a non-VARI Privacy Board or IRB will be reviewed by the VARI IRB.

16.3 Authorization

Except as otherwise permitted, the Privacy Rule requires that covered entities obtain authorization from research subjects for the use or disclosure of his/her PHI to be utilized in the research. This authorization is distinct from the subject's consent to participate in research, which is required under the Common Rule and FDA regulations. Just as a valid consent under Common Rule and FDA regulations must meet certain requirements, a valid authorization must contain certain statements and core elements (45 CFR 164.508(c)).

Once executed, a signed copy must be provided to the individual providing authorization. Signed authorizations must be retained by the PI and the covered entity (e.g., the clinical site) for 6 years from the date of creation or the date it was last in effect, whichever is later.

A research subject has the right to revoke their authorization at any time. Researchers are not required to retrieve information that was disclosed under the authorization before learning of the revocation. Additionally, researchers may continue to use and disclose PHI already obtained for the research under an authorization to the extent necessary to protect the integrity of the research.

When an Authorization permits disclosure of PHI to a person or organization that is not a covered entity (such as a sponsor or funding source of the research), the Privacy Rule does not continue to protect the PHI disclosed to such entity. However, other Federal and State laws may establish continuing protections for the disclosed information. Under the HHS or the FDA Protection of Human Subjects Regulations, an IRB may impose further restrictions on the use or disclosure of research information to protect subjects.

Authorization Core Elements:

1. A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner.
2. The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure.
3. The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure.
4. A description of each purpose of the requested use or disclosure.
5. Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure ("end of the research study" or "none" are permissible for research, including for the creation and maintenance of a research database or repository).

6. Signature of the individual and date. If the individual's legally authorized representative (LAR) signs the Authorization, a description of the representative's authority to act for the individual must also be provided.

Authorization Required Statements:

1. A statement of the individual's right to revoke his/her Authorization and how to do so, and, if applicable, the exceptions to the right to revoke his/her Authorization or reference to the corresponding section of the covered entity's notice of privacy practices.
2. Whether treatment, payment, enrollment, or eligibility of benefits can be conditioned on Authorization, including research-related treatment and consequences of refusing to sign the Authorization, if applicable.
3. A statement of the potential risk that PHI will be re-disclosed by the recipient. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.

16.4 Waiver or Alteration of the Authorization Requirement

Obtaining signed authorization to access and use PHI for research is not always feasible. The Privacy Rule contains criteria for waiver or alterations of authorization.

For research uses and disclosures of PHI, an IRB or Privacy Board may approve a waiver or an alteration of the Authorization in whole or in part. A complete waiver occurs when the IRB or Privacy Board determines that no authorization will be required for a covered entity to use and disclose PHI for a particular research project. A partial waiver of Authorization occurs when the IRB or Privacy Board determines that the institution does not need authorization for PHI uses and disclosures for research purposes, such as accessing PHI for research recruitment purposes. An IRB or Privacy Board may also approve a request that removes some PHI, but not all, or alters the requirements for an Authorization (an alteration).

In order for an IRB or Privacy Board to waive or alter authorization, the Privacy Rule (45 CFR 164.512(i)(2)(ii)) requires the IRB or Privacy Board to determine the following:

- The use or disclosure of PHI involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
  - An adequate plan to protect health information identifiers from improper use and disclosure.
  - An adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so).
  - Adequate written assurances that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.
- The research could not practicably be conducted without the waiver or alteration or Authorization.

- The research could not practicably be conducted without access to and use of the PHI.

The Privacy Rule allows institutions to rely on a waiver or an alteration of Authorization obtained from a single Privacy Board to be used to obtain or release PHI in connection with a multi-site project. However, HHS also recognizes that "covered entities may elect to require duplicate Privacy Board reviews before disclosing [PHI] to requesting researchers" (67 *Federal Register* 53232, August 14, 2002). At VARI, PHI may not be disclosed for the purposes of research pursuant to a waiver provided by a non-VARI Privacy Board without the approval of the VARI IRB.

VARI IRB documentation of approval of a waiver or alteration of the authorization includes:

- The identity of the approving IRB;
- The date on which the waiver or alteration was approved;
- A statement that the IRB has determined that all the specified criteria for a waiver or an alteration were met;
- A brief description of the PHI for which use or access has been determined by the IRB to be necessary in connection with the specific research activity;
- A statement that the waiver or alteration was reviewed and approved under either normal or expedited review procedures; and
- The required signature of the IRB chair or the chair's designee.

16.5 Future Uses: Databases and Repositories

The Privacy Rule recognizes the creation of a research database or a specimen repository to be a research activity if the data/specimens to be stored contain PHI. There are two separate activities that the covered entity must consider: (1) the use or disclosure of PHI for creating a research database or repository and (2) the subsequent use or disclosure of PHI in the database for a particular research protocol.

Individual authorization for the storage of PHI for future research must be sought unless the IRB has determined that the criteria for a waiver of the authorization requirement are satisfied. See *Section 16.4* of this policy manual for a discussion of waivers of authorization.

While VARI is not a covered entity itself, the clinical entities with which VARI researchers commonly collaborate typically combine consent for research and authorization for use and/or disclosure of PHI in one document. As with any research activity, the combined consent/authorization for future research must describe the future research uses in sufficient detail to allow the potential subject to make an informed decision. The researcher and IRB should be cognizant of uses of information/specimens that the target community may consider particularly sensitive, such as genetics, mental health, studies of origin, and use of tissues that may have cultural significance.

The consent/authorization for future research can be a stand-alone document or may be incorporated into another consent/authorization if the information/specimens will originate from another research activity, such as a clinical trial, unless the research involves the use or

disclosure of psychotherapy notes. Authorizations for the use or disclosure of psychotherapy notes can only be combined with another authorization for a use or disclosure of psychotherapy notes.

If the consent/authorization for future research is combined with another research consent/authorization, the consent/authorization must clearly differentiate between the research activities and allow the individual to opt-in to the future research. Opt-outs for future research are not permitted under the Privacy Rule because an opt-out process does not provide individuals with a clear ability to authorize the use of their information/specimens for future research, and may be viewed as coercive.

16.6 Corollary and Sub-studies

As with any other research, subject participation in corollary or sub-studies not essential to the primary aims of the research should be on a voluntary basis. This is particularly important when the primary research offers a potential benefit, such as treatment, that might compel the potential subject to agree to something that they otherwise would not.

HIPAA reinforces this ethical principle by explicitly stating that authorization for "unconditioned" activities, for which there is no associated treatment, benefit or other effect on the individual subject associated with participation, cannot be required. The published preamble to HIPAA Omnibus clarifies the basis for this position, and the requirement that authorization for unconditioned activities involve a clear opt-in mechanism, stating:

"This limitation on certain compound authorizations was intended to help ensure that individuals understand that they may decline the activity described in the unconditioned authorization yet still receive treatment or other benefits or services by agreeing to the conditioned authorization." and "an opt out option does not provide individuals with a clear ability to authorize the optional research activity, and may be viewed as coercive by individuals."

As with authorization for future research, it is acceptable to combine in a single document the authorization for a conditioned activity, such as a clinical trial, with authorization for an unconditioned activity such as a corollary or sub-study that does not directly benefit or effect the individual participant, provided that:

- The authorization clearly differentiates between the conditioned and unconditioned research activities;
- The authorization clearly allows the individual the option to opt-in to the unconditioned research activities; and
- Sufficient information is provided for the individual to be able to make an informed choice about both the conditioned and unconditioned activities.

Separate authorization must be obtained for each research activity that involves the use and disclosure of psychotherapy notes. For example, authorization for the use and disclosure of psychotherapy notes for a clinical trial cannot be combined with an authorization for the use and disclosure of those psychotherapy notes for a corollary research activity.

16.7 De-identification of PHI under the Privacy Rule

Covered entities may use or disclose health information that is de-identified without restriction under the Privacy Rule. The "Safe Harbor" method permits a covered entity to de-identify data by removing all 18 elements that could be used to identify the individual or the individual's relatives, employers, or household members. The covered entity also must have no actual knowledge that the remaining information could be used alone or in combination with other information to identify individuals. Under this method, the identifiers that must be removed are the following:

1) Names.
2) All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:
    a. The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people.
    b. The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.
3) All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.
4) Telephone numbers.
5) Facsimile numbers.
6) Electronic mail addresses.
7) Social security numbers.
8) Medical record numbers.
9) Health plan beneficiary numbers.
10) Account numbers.
11) Certificate/license numbers.
12) Vehicle identifiers and serial numbers, including license plate numbers.
13) Device identifiers and serial numbers.
14) Web universal resource locators (URLs).
15) Internet protocol (IP) address numbers.
16) Biometric identifiers, including fingerprints and voiceprints.
17) Full-face photographic images and any comparable images.

18) Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.

Alternatively, a qualified statistician may certify that the risk is very small that health information could be used, alone or in combination with other available information, to identify individuals. The qualified statistician must document the methods and results of the analysis that justify such a determination. This analysis must be retained by the covered entity for 6 years from the date of its creation or when it was last acted on, whichever is later.

The Privacy Rule permits a covered entity to assign to, and retain with, the de-identified health information, a code or other means of record re-identification if that code is not derived from or related to the information about the individual and is not otherwise capable of being translated to identify the individual. The covered entity may not use or disclose the code or other means of record identification for any other purpose and may not disclose its method of re-identifying the information.

NOTE: Data that is considered de-identified under HIPAA may still be considered human subjects data under the Common Rule, particularly when working with a small data set that can be further broken down into smaller subsets. Additionally, while coded information may be de-identified under HIPAA, if the researcher holds or has the ability to access both the code and the data, the information is considered identifiable private information under the Common Rule.

16.8 Limited Data Sets and Data Use Agreements

Limited data sets (LDS) are data sets stripped of certain direct identifiers. LDSs may be used or disclosed only for public health, research, or health care operations purposes. Because LDSs may contain identifiable information, they are still PHI and as such are not considered de-identified under the Privacy Rule. Unlike de-identified data, PHI in LDSs may include: addresses other than street name or street address or post office boxes, all elements of dates (such as admission and discharge dates) and unique codes or identifiers not listed as direct identifiers. The following direct identifiers must be removed for PHI to qualify as a LDS: (1) Names; (2) postal address information, other than town or city, state, and ZIP code; (3) telephone numbers; (4) fax numbers; (5) email addresses; (6) social security numbers; (7) medical record numbers; (8) health plan beneficiary numbers; (9) account numbers; (10) certificate or license numbers; (11) vehicle identifiers and license plate numbers; (12) device identifiers and serial numbers; (13) URLs; (14) IP addresses; (15) biometric identifiers; and (16) full-face photographs and any comparable images.

Before disclosing an LDS a covered entity must enter into a data use agreement (DUA) with the recipient, even when the recipient is a member of its workforce. The DUA establishes the parameters around the proposed uses and disclosures of the data, who is permitted to have access to the data, and stipulates that no other use will be made of the data, no attempt will be made to identify or contact individuals whose data are included in the LDS, that appropriate safeguards are in place to protect the data from unauthorized use and that the recipient will report any uses or disclosures of the PHI that they become aware of that not in keeping with the terms of the DUA.

While VARI is not a covered entity, investigators at VARI will abide by any written agreements with any covered entity, including DUAs, when applicable.

16.9 Research Subject Access to PHI

With few exceptions, the Privacy Rule guarantees individuals access to their medical records and other types of health information. One exception is during a clinical trial, when the subject's right of access can be suspended while the research is in progress. The subject must have been notified of and agreed to the temporary denial of access when providing consent and authorization. Any such notice must also inform the individual that the right to access will be restored upon conclusion of the clinical trial.

17 Information Security

VARI has established standards and safeguards to protect research subject's information and to ensure compliance with federal and state information security regulations. It is the responsibility of investigators to familiarize themselves with and comply with these standards. The use of personal laptops, desktops, USB drives, and other non-VARI devices for storage of research data is discouraged. In the instances when a non-VARI computer or device must be utilized for the purposes of storing, even temporarily, or transmitting PHI or PII (Personally Identifiable Information) for research, the safeguards of the device must be verified by Information Technology Department and a User Agreement must be completed. Additionally, any potential or known breach of research data or a device storing research data must be immediately reported to both the IRB, the Compliance Department and the HIPAA Security Officer so that appropriate steps can be taken to assess the situation, protect the information, and comply with regulations. Lost or stolen VARI devices must also be reported to the Physical Security and IT Departments, so that tracking mechanisms to remotely wipe or protect data can be activated.

Provisions for Data Security must be described in applications to the IRB and updated as necessary. When information containing direct identifiers such as Social Security Numbers or PHI including data considered sensitive is to be transferred outside of VARI, the provisions for data security may be subject to further review and approval by the HIPAA Security Officer.

Sensitive information refers to data or information, on any storage media or in any form or format, which requires protection due to the risk of harm that could result from inadvertent or deliberate disclosure, unauthorized access, misuse, alteration, or loss or destruction of the information.

See the VARI Information Technology Policies on SharePoint for further information.

18 Repositories and Research Involving Biological Specimens or Coded Human Data

18.1 Biological Specimens

All activities involving the collection of human biological specimens for research purposes, as well as the research use of specimens collected for clinical care, must be conducted under the terms of an IRB-approved research protocol. The collection and use of human biological specimens (either identifiable or de-identified) must comply with all applicable laws and regulations for research involving human biological specimens or superseding requirements.

18.1.1 Regulatory Oversight

Under HHS regulations, a human subject is a living individual about whom an investigator conducting research obtains:

- Data through intervention or interaction with the individual; or
- Identifiable private information.

Whether research involving biological specimens meets the definition of human subjects research is based on: a) how the specimens were obtained; and b) whether the specimens include identifiable private information.

If the specimens are obtained specifically for research purposes, then they have been collected through intervention or interaction with the individual and, thus, the research meets the definition of human subjects research. If the specimens were not collected for research purposes but as part of routine clinical care or other non-research purpose, then the research only meets the definition of human subjects research if the specimens include identifiable private information (See below for policies on coded specimens).

FDA regulations do not apply to biological specimens unless they are gathered as part of a clinical investigation involving human subjects or being used to test a medical device (See *Section 9* for more detail on FDA regulations). HIPAA does not directly address biological specimens but does apply to protected health information (PHI) linked to the specimens (See *Section 16* for more detail on HIPAA). In addition, per the Newborn Screening Saves Lives Reauthorization Act of 2014 (Public Law No: 113-240), federally-funded research funded using newborn dried spots is considered human subjects research regardless of whether the specimens are identifiable. Further, the law eliminates the ability of the IRB to approve alterations or waivers of informed consent under 45 CFR 46.116(c) and 116(d) for research involving newborn dried blood spots.

State and local laws will also be considered and followed.

If the research meets the definition of human subjects research, then all of the requirements of this document apply.

18.1.2 IRB Review

- Research involving only biological specimens may be exempt under Exemption Category #4: "Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available, or if the information is recorded by the investigator in such a manner that subjects cannot be identified directly or through identifiers linked to the subjects." However, in order to qualify under this category, all of the specimens must exist prior to the research being submitted to the IRB.
- Non-exempt research only involving biological specimens may be eligible for expedited review if it is minimal risk and falls within one of the following categories:
  - Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture [with restrictions]
  - Prospective collection of biological specimens for research purposes by noninvasive means.
  - Research involving materials that have been collected, or will be collected solely for non-research purposes
- All non-exempt research involving biological specimens that are not eligible for expedited review must be reviewed at a convened IRB meeting.
- For all non-exempt research involving biological specimens, informed consent and documentation of consent is required unless waived by the IRB.

18.2 Coded Human Data or Biological Specimens

This section is based on the OHRP guidance document entitled, "Guidance on Research Involving Coded Private Information or Biological Specimens" (October 16, 2008). This document:

1. Provides guidance as to when research involving coded private information or specimens is or is not research involving human subjects, as defined under HHS regulations for the protection of human research subjects (45 CFR part 46).

2. Reaffirms OHRP policy that, under certain limited conditions, research involving ***only*** coded private information or specimens is not human subjects research.

3. Clarifies the distinction between (a) research involving coded private information or specimens that do not involve human subjects and (b) human subjects research that is exempt from the requirements of the HHS regulations.

4. References pertinent requirements of the HIPAA Privacy Rule that may be applicable to research involving coded private information or specimens.

Note: The FDA definition of human subjects differs from the Common Rule definition. Use of coded specimens for FDA-regulated research such as research on In Vitro Diagnostic Devices requires assessment according to the FDA regulations and guidelines. Investigators should contact the IRB office for guidance.

For purposes of this policy, ***coded*** means that: (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens. At VARI, research with specimens with one-way linkages maintained by an investigator outside of VARI is considered human subjects research.

Guidance:

Obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research. ***Obtaining*** identifiable private information or identifiable specimens includes, but is not limited to:

1. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to the investigator from any source; and

2. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that were already in the possession of the investigator.

In general, private information or specimens are considered to be individually identifiable when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Private information or specimens are not considered to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Research involving **only** coded private information or specimens do **not** involve human subjects per the Common Rule definition if both of 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 investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are

deceased (note that the HHS regulations do not require the IRB to review and approve this agreement) At VARI, this agreement must be reviewed and approved by the IRB.

b. There are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or

c. There are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased. While decedents are not considered "human subjects" under the Common Rule, other requirements and regulations, such as HIPAA, may still apply. Investigators should contact the VARI IRB office with any questions regarding research using decedent information and/or specimens.

In some cases an investigator who obtains coded private information or specimens about living individuals under one of the conditions cited in 2(a)-(c) above may (1) unexpectedly learn the identity of one or more living individuals, or (2) for previously unforeseen reasons now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained private information or specimens pertain, then the research activity now would involve human subjects. Unless this human subjects research is determined to be exempt (See *Section 3.3*), IRB review of the research would be required. Informed consent of the subjects also would be required unless the IRB approved a waiver of informed consent (See *Section 7.9*).

18.2.1 Who Should Determine Whether Coded Private Information or Specimens Constitutes Human Subjects Research

The investigator in consultation with the IRB Chair or IRB Compliance Specialist will determine if the research involving coded information or specimens requires IRB review.

A **repository** is a collection of data or biological specimens whose organizers:

- Receive data or specimens from multiple sources;
- Maintain the data or specimens over time; and
- Control access to and use of data or specimens by multiple individuals and/or for multiple purposes, which may evolve over time.

These policies and procedures apply to both data and biological sample repositories. For simplicity, both will be referred to as samples in this document.

There are two types of repositories:

- Non-research repositories created and maintained for purposes that are totally unrelated to research. Such purposes may include diagnosis, treatment, billing, marketing, quality control, and public health surveillance.

- Research repositories created and maintained specifically for research purposes. Such purposes may include databases to identify prospective subjects, patient outcome information to evaluate treatment effectiveness, and tissue samples for future research

18.2.2 Non-research Repositories

Even though repositories were not created for research purposes, they may contain information that is of great interest to researchers. The creation (or operation) of non-research databases or repositories do not involve human subject research and do not require IRB oversight. However, IRB oversight is required for use in research of identifiable private information or identifiable human specimens from non-research databases and repositories (including data/tissue banks and registries).

- When research involves identifiable private information or identifiable human specimens, each research use must receive prospective IRB review and approval and continuing IRB oversight.
- Researchers should submit an application for IRB review and receive IRB approval before initiating the research.
- Where available, the application should include any available information about the circumstances under which the information or specimens were originally collected.
- Investigators who believe their research may be exempt from the human subject regulations should include a request for exemption with the *Exempt Research Application (HRPP-FORM-007)*.
- The IRB may require researchers obtain the informed consent of subjects for research involving information or specimens contained in non-research databases or repositories. The IRB can waive the requirement for informed consent if the research meets the waiver criteria in the regulations.

18.2.3 Research Repositories

Research repositories involve three primary components:

- The collection of samples;
- The storage and data management center; and
- The recipient investigators.

18.2.3.1 Sample collection

If the samples were collected for research purposes or are associated with information that can identify the donor, then Informed consent must be obtained from the donor unless appropriately waived by the IRB.

Informed consent information should include:

- A clear description of:
  - The operation of the database;
  - The types of research to be conducted;
  - The conditions under which data will be released to recipient-investigators; and
  - Procedures for protecting the privacy of subjects and maintaining the confidentiality of data.
- A statement regarding future withdrawal of data or specimens from the research repository (i.e., state whether subjects may, in the future, request that their data be removed or specimens be destroyed).

Other information, such as the length of time that data will be stored, subjects' access to information learned from the research, and secondary uses of the samples should be considered, as appropriate.

Repositories should have data submission policies to ensure that the data was collected in an ethical manner, such as informed consent and IRB approval.

18.2.3.2 Sample Storage and Management

Repositories should have written policies on:

- Data and tissue submission requirements
  - Informed consent
  - IRB review
- Physical and procedural mechanisms for the secure receipt, storage, and transmission of information and specimens, including chain-of-custody.
- Policies on release of information and specimens
  - Coding
  - Release of identifiers
  - Certificates of Confidentiality

18.2.3.3 Recipient Investigators

Recipient-investigators should have a written agreement with the repository. The written agreement should specify under what conditions the data is being released to the recipient-investigator(s). The terms under which the data is released determine whether the research requires IRB oversight.

18.2.4 IRB Oversight

Operation of a research repository and its data management center under the auspices of VARI is subject to oversight by the VARI IRB. Proposals to establish a repository must be submitted to the IRB using the *IRB Application Form (HRPP-FORM-001)* specifying the conditions under which data and specimens may be accepted and shared, and ensuring adequate provisions to protect the privacy of subjects and maintain the confidentiality of data. The IRB also reviews and approves the repository protocol that describes the collection process, informed consent document and process, researcher request and approval process to provide specimens and/or data, and any requirements for approval from external IRBs.

18.2.5 HIPAA

PHI held by a covered entity in non-research repositories may not be used or disclosed for research purposes without written authorization or an IRB waiver of authorization. The IRB review process should include how and what information will be given when proposing to provide de-identified specimens.

HIPAA applies to submission of PHI to a research repository and authorization is required when appropriate. See *Section 16* for a detailed discussion of authorization, waivers, limited data sets, and de-identification. HIPAA allows authorization for future research when sufficient information is provided to the subject on potential future research scope (e.g., research on cancer, Alzheimer's disease, and other chronic diseases, including their genetic basis), but that also enables the subject to be able to make an informed choice. Authorization for future research can be combined with an authorization for other research activities as described in *Sections 16.5* and *16.6*.

19 Special Topics

19.1 Certificate of Confidentiality (CoC)

Certificates of Confidentiality (CoCs) are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. CoCs allow the PI and others who have access to research records to refuse to disclose identifying information on research subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. A CoC does not protect against voluntary disclosures by the researcher, but those disclosures must be specified in the informed consent form. A researcher may not rely on the CoC to withhold data if the participant consents in writing to the disclosure.

Generally, any research project that collects personally identifiable, sensitive information and that has been approved by an IRB operating under either an approved Federal-Wide Assurance issued by the Office of Human Research Protections or the approval of the Food and Drug Administration is eligible for a CoC. Federal funding is not a prerequisite for a NIH-issued CoC, but the subject matter of the study must fall within a mission area of the NIH, including its Institutes, Centers, and the National Library of Medicine.

19.1.1 Statutory Basis for Protection

Protection against compelled disclosure of identifying information about subjects of biomedical, behavioral, clinical, and other research is provided by the Public Health Service (PHS) Act §301(d), 42 U.S.C. §241(d):

"The Secretary may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, including research on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research, the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals."

19.1.2 Usage

CoCs may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, CoCs help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to subjects.

Any PI engaged in research in which sensitive information is gathered from human subjects (or any person who intends to engage in such research) may apply for a CoC. Research can be considered "sensitive" if it involves the collection of:

- Research on Human Immunodeficiency Virus (HIV), Acquired Immunodeficiency Syndrome (AIDS), and Sexually Transmitted Diseases (STDs);

- Information about sexual attitudes, preferences, practices;
- Information about personal use of alcohol, drugs, or other addictive products;
- Information about illegal conduct;
- Information that could damage an individual's financial standing, employability, or reputation within the community;
- Information in a subject's medical record that could lead to social stigmatization or discrimination; or
- Information about a subject's psychological well-being or mental health.
- Genetic studies, including those that collect and store biological samples for future use;
- Research on behavioral interventions and epidemiologic studies.

This list is not exhaustive. Researchers contemplating research on a topic that might qualify as sensitive should contact the IRB Office for assistance in applying for a CoC.

In the consent form, PIs should tell research subjects that a CoC is in effect. Subjects should be given a fair and clear explanation of the protection that a CoC affords, including the limitations and exceptions noted above. Every research project that includes human research subjects should explain how identifiable information will be used or disclosed, regardless of whether a CoC is in effect.

19.1.3 Limitations

The protection afforded by a CoC is not absolute. A CoC protects research subjects only from legally compelled disclosure of their identity. It does not restrict voluntary disclosures.

For example, a CoC does not prevent researchers from voluntarily disclosing to appropriate authorities such matters as child abuse, a subject's threatened violence to self or others, or from reporting a communicable disease. However, if researchers intend to make such disclosures, this should be clearly stated in the consent form which research subjects are asked to sign.

In addition, a CoC does not authorize the person to whom it is issued to refuse to reveal the name or other identifying characteristics of a research subject if:

- The subject (or, if incompetent, his or her guardian) consents, in writing, to the disclosure of such information;
- Authorized personnel of the HHS request such information for audit or program evaluation, or for investigation of HHS grantees or contractors and their employees; or
- Release of such information is required by the Federal Food, Drug, and Cosmetic Act or regulations implementing that Act.

Finally, ambiguity remains as to whether a CoC would prevent disclosure in situations involving government audits, law enforcement, and foreign treatment of the rule not mentioned above. Accordingly, the total protection offered by the CoC is at present uncertain.

19.1.4 Application Procedures

Any person engaged in research collecting sensitive information from human research subjects may apply for a CoC. For most research, CoCs are obtained from NIH. If NIH funds the research project, the PI may apply through the funding Institute. However, even if the research is not supported by NIH funding, the PI may apply for a CoC through the NIH Institute or Center (IC) funding research in a scientific area similar to the project.

If the research being conducted is a sensitive research project that is covered by the Agency for Healthcare Research and Quality (AHRQ) confidentiality statute (42 U.S.C. section299a-1(c) entitled "limitation on use of certain information") or the Department of Justice confidentiality statute (42USC section 3789g), then a CoC is not required.

If there is an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE), the sponsor can request a CoC from the FDA.

For more information, see the NIH Certificates of Confidentiality Kiosk (http://grants.nih.gov/grants/policy/coc/index.htm).

19.2 Mandatory Reporting

While any person may make a report if they have reasonable cause to believe that a child or elder was abused or neglected, Michigan law mandates that certain persons who suspect child or elder abuse or neglect report this to the Michigan Department of Health and Human Services.

In situations where conditions of abuse or neglect might be revealed, mandated reporters should make themselves known via the consent process and form to parents of children under age 18, to subjects who are children, and to subjects who are potential victims of abuse or neglect. Michigan Compiled Law (MCL) 722.623 outlines the individuals required to report child abuse under the Michigan Child Protection Law. MCL 400.11a outlines the individuals required to report adult/elder abuse and neglect under the Michigan Social Welfare Act.

19.3 Additional Researcher Obligations

A researcher using a CoC has an affirmative obligation to inform all research subjects whether the CoC applies. Once a CoC has been acquired, the researcher is required to "support and defend" the authority of the CoC.

19.4 VARI Students and Employees as Subjects

When VARI students and/or employees are being recruited as potential subjects, researchers must ensure that there are additional safeguards for these subjects. The voluntary nature of their participation must be primary and without undue influence on their decision. Researchers must emphasize to subjects that their academic status, grades, or their employment, will be affected by their decision to participate or not.

To minimize coercion, PIs should avoid, whenever possible, the use of their students and employees in procedures which are neither therapeutic nor diagnostic in nature. In these latter

situations, PIs should solicit subjects through means such as bulletin board notices, flyers, advertisements in newspapers, and announcements in classes or laboratories other than their own. When entering a classroom to recruit students and conduct research, e.g. administer a survey, PIs should do so at the end of the class period to allow non-participating students the option of leaving the classroom, thereby alleviating pressure to participate.

19.5 Student Research

19.5.1 Human Subjects Research and Course Projects

Learning how to conduct ethical human subjects research is an important part of a student's educational experience. Research activities that are designed as part of a course requirement for purposes of learning experience only and are NOT *designed to develop or contribute to generalizable knowledge* may not require IRB review and approval if all of the following conditions are true:

- Results of the research are viewed only by the course instructor for teaching purposes and discussed within the classroom for teaching and learning purposes.
- Results of the research are not made public through presentation (outside of the classroom) and are not published in paper or electronic format (e.g., not made available on the internet, not published in a journal, etc.).
- Research procedures are no more than minimal risk.
- Vulnerable populations are not targeted (e.g., children under age 18, prisoners, persons who are cognitively impaired, etc.).
- Data collected are recorded in such a manner that the subjects are not identifiable. Images in videotapes and photographs, and voices on audiotape are considered identifiable.
- When appropriate, an informed consent process is in place.

Responsibility of the Course Instructor: The course instructor is responsible for communicating to the students, the ethics of human subjects research, for ensuring the protection of human subjects (including that a process is in place for obtaining voluntary informed consent from research subjects when appropriate), and for monitoring the students' progress.

When designing a project, students should be instructed on the ethical conduct of research and on the preparation of the IRB application when such is required. In particular, instructors and students should:

- Understand the elements of informed consent;
- Develop appropriate consent documents;
- Plan appropriate strategies for recruiting subjects;
- Identify and minimize potential risks to subjects;
- Assess the risk-benefit relationship for the project;

- Establish and maintain strict guidelines for protecting confidentiality, and
- Allow sufficient time for IRB review (if necessary) and completion of the project.

In making a determination of whether or not a class research project requires IRB review, the instructor should err on the side of caution and to contact the IRB office for assistance.

Individual Research Projects Conducted by Students. Independent study projects, senior theses, undergraduate research projects, masters and advanced degree research, and similar exercises must be independently submitted for IRB review. It is important to keep in mind that any human subjects research activity that will ultimately contribute to part or all of a thesis, dissertation, or other type of publication or presentation must go through the IRB review process prior to enrolling subjects and collecting data. IRB review cannot occur after a study has begun.

Students and advisors should contact the IRB Office with any questions.

19.5.2 Independent Study, Theses and Dissertations

These research activities are considered to meet the federal definition of human subjects research and must be independently submitted to the IRB by the student-researcher. However, when students conduct research as part of a course of study, *a faculty member ultimately is responsible for the protection of the subjects*, even if the student is the primary researcher and actually directs the project. Advisers assume the responsibility for students engaged in independent research, and instructors are responsible for research that is conducted as part of a course.

Students may not serve as PI. They must have a faculty sponsor who fulfills the PI eligibility criteria and who will serve as PI and faculty advisor on the study. (See *Section 15.1.1*)

19.6 Oral History

The following is based on guidance received from OHRP:

A decision whether oral history or other activities solely consisting of open ended qualitative type interviews are subject to the policies and regulations outlined in VARI's FWA and HHS regulations for the protection of human research subjects (45 CFR 46) is based on the prospective intent of the investigator and the definition of "research" under HHS regulations at 45 CFR 46.102(d): "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

Specifically, for the purposes of this policy, the evaluation of such activities hinges upon whether:

- The activity involves a prospective research plan which incorporates data collection, including qualitative data, and data analysis to answer a research question; and
- The activity is designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.

In order to be subject to VARI's human research protections policies, the activity must meet both of the above standards. This determination will be made according to the procedures described in *Section 3.2*.

General principles for evaluating Oral History activities:

1. Oral History activities, such as open ended interviews, that only documents a specific historical event or the experiences of individuals without intent to draw conclusions or generalize findings would not constitute "research" as defined by HHS regulations at 45 CFR 46.

   Example: An Oral History video recording of interviews with holocaust survivors is created for viewing in the Holocaust Museum. The creation of the video tape does not intend to draw conclusions, inform policy, or generalize findings. The sole purpose is to create a historical record of specific personal events and experiences related to the Holocaust and provide a venue for Holocaust survivors to tell their stories.

2. Systematic investigations involving open-ended interviews that are designed to develop or contribute to generalizable knowledge (e.g., designed to draw conclusions, inform policy, or generalize findings) would constitute "research" as defined by HHS regulations at 45 CFR 46.

   Example: An open ended interview of surviving Gulf War veterans to document their experiences and to draw conclusions about their experiences, inform policy, or generalize findings.

3. Oral historians and qualitative investigators may want to create archives for the purpose of providing a resource for others to do research. Since the intent of the archive is to create a repository of information for other investigators to conduct research as defined by 45 CFR 46, the creation of such an archive would constitute research under 45 CFR 46.

   Example: Open ended interviews are conducted with surviving Negro League Baseball players in order to create an archive for future research. The creation of such an archive would constitute research under 45 CFR 46 since the intent is to collect data for future research.

   Investigators are advised to consult with the IRB Office to determine whether their Oral History project requires IRB review.

19.7 Genetic Studies

Genetic research studies may create special risks to human subjects and their relatives. These involve medical, psychosocial, and economic risks, such as the possible loss of privacy, insurability, and employability, change in immigration status and limits on education options, and may create a social stigma. Knowledge of one's genetic make-up may also affect one's knowledge of the disease risk status of family members.

In studies involving genetic testing, several questions need to be addressed (*IRB application Form* in *Supplement H*, including:

- Will test results be provided to the subjects?
- Will disease risk be quantified, including the limits on certainty of the testing?
- Will a change in a family relationship be disclosed, such as mistaken paternity?
- Does the subject or family member have the option not to know the results? How will this decision be recorded?
- Could other clinically relevant information be uncovered by the study? How will disclosure of this added information occur?
- Do any practical limitations exist on the subject's right to withdraw from the research, withdraw data, and/or withdraw DNA?
- Is the subject permitted to participate in the study while refusing to have genetic testing (such as in a treatment study with a genetic testing component)?

For studies involving DNA banking, several questions need to be addressed (IRB application form in Supplement H), including:

- Will DNA be stored or shared? If shared, will the subject's identity be known by the recipient investigator?
- Will the subject be contacted in the future by the investigator to obtain updated clinical information?
- How can the subject opt out of any distribution or subsequent use of his/her genetic material?

For information on incidental findings, see S*ection 19.10.*

19.8 Case Reports Requiring IRB Review

Although VARI does not have a clinical center, in general, an anecdotal report on a small series of patients seen in a clinician's private practice and a comparison of these patients to existing reports in the literature is not research and would not require IRB approval. Going beyond one's own practice to seek out and report cases seen by other clinicians creates the appearance of a systematic investigation with the intent to contribute to generalizable knowledge and therefore would be considered research and would require IRB approval.

19.8.1 Definitions

Single Case Report. The external reporting (e.g., publication or poster/verbal presentation) of an interesting clinical situation or medical condition of a single patient. Case reports normally contain detailed information about an individual patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The patient information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.

Case Series. The external reporting (e.g., publication or poster/verbal presentation) of an interesting clinical situation or medical condition in a series of patients (i.e., more than one patient). Case series usually contain detailed information about each patient and may include demographic information and information on diagnosis, treatment, response to treatment, post treatment follow-up, as well as a discussion of existing relevant literature. The information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.

19.9 International Research

The IRB will review all international research utilizing human subjects to assure adequate provisions are in place to protect the rights and welfare of the subjects. Approval of research is permitted if "the procedures prescribed by the foreign institution afford protections that are at least equivalent to those provided in 45 CFR 46." All policies and procedures that are applied to research conducted domestically should be applied to research conducted in other countries, as appropriate.

For international research, VARI IRB seeks sufficient knowledge of the local research context by requesting approval for the project from local IRBs or Ethics Committees (EC), which may or may not hold an approved FWA, and/or local letters of support. The source of this information will depend on the nature of the study, on the country, and on the resources available to the PI. Where there is a local IRB/EC, VARI IRB must receive and review the foreign institution or site's IRB/EC review and approval of each study prior to the commencement of the research at the foreign institution or site.

In some circumstances where research may be performed internationally and/or in settings where there are no IRBs, the VARI IRB may, prior to approval of the research, require additional verification and information from people outside the particular research project who are familiar with the customs, practices, or standards of care where the research will be taking place, such as local IRBs or ECs, other VARI researchers with knowledge of the region, or other experts on the region. These individuals may either provide a written review of a particular protocol or attend an IRB meeting to provide VARI IRB with recommendations based on his or her expertise.

For Federally funded research, approval of research for foreign institutions or sites "engaged" in research is only permitted if the foreign institution or site holds an Assurance with OHRP and local IRB review and approval is obtained.

For DoD funded research, investigators are required to provide written approval from the Research Ethics Board (REB) or IRB equivalent at the international site that the proposed research project can be conducted. In addition, at VARI, the protocol will be reviewed using the *DoD IRB Reviewer Checklist* HRPP-CHK-020.01. The investigator is required to acknowledge having read the Department of Defense Instruction 3216.02 and indicateagreement to follow the requirements for conducting international research involving DoD funds. Depending on the nature of the research, continuation reports may be required more frequently than annually. In the event of a greater than minimal risk study, research monitors are required, need to be identified and approved by the DoD, IRB and REB. It should be noted that based on VARI's

research portfolio, it is highly unlikely that greater than minimal risk studies will be conducted abroad by VARI investigators.

Approval of research for foreign institutions or sites "not engaged" in research is only permitted if one or more of the following circumstances exist:

- When the foreign institution or site has an established IRB/EC, the Investigator must obtain approval to conduct the research at the "not engaged" site from the site's IRB/EC or provide documentation that the site's IRB/EC has determined that approval is not necessary for the Investigator to conduct the proposed research at the site.
- When the foreign institution or site does not have an established IRB/EC, a letter of cooperation must be obtained demonstrating that the appropriate institutional or oversight officials are permitting the research to be conducted at the performance site.
- IRB approval to conduct research at the foreign institution or site is contingent upon receiving documentation of the performance site's IRB/EC determination, or letter of cooperation, as applicable.

19.9.1 Responsibilities

It is the responsibility of:

- VARI investigator and the foreign institution or site to assure that the resources and facilities are appropriate for the nature of the research.
- VARI investigator and the foreign institution or site to confirm the qualifications of the researchers and research staff for conducting research in that country(ies).
- VARI investigator and the foreign institution or site to ensure that the following activities will occur:
  - Initial review, continuing review, and review of modification
  - Post-approval monitoring
  - Handling of complaints, non-compliance and unanticipated problems involving risk to subjects or others.
- VARI investigator and the foreign institution or site to notify the IRB promptly if a change in research activities alters the performance site's engagement in the research (e.g., performance site "not engaged" begins consenting research subjects, etc.).

VARI IRB will not rely on a local ethics committee that does not have policies and procedures for the activities listed above.

19.9.2 Consent Documents

The informed consent documents must be in a language understandable to the proposed subjects, see *Section 7.7.1*.

19.9.3 Monitoring of Approved International Research

The IRB is responsible for the ongoing review of international research conducted under its jurisdiction through the continuing review process in accordance with all applicable federal regulations.

When the IRB and a local ethics committee will both be involved in the review of research, there is a plan for coordination and communication with the local IRB/ECs.

The IRB will require documentation of regular correspondence between the VARI Investigator and the foreign institution or site and may require verification from sources other than the VARI Investigator that there have been no substantial changes in the research since its last review.

19.10 Incidental Findings

In developing research, investigators should consider the types and likelihood of incidental findings that may occur and plan accordingly. Likewise, the IRB should consider the same in conducting its review and ensuring that human subjects are appropriately protected. Not all incidental findings, however, can be anticipated, and investigators and IRBs must be prepared to consider such findings and take action as appropriate, given the circumstances. The following summarizes recommendations specific to research that are included in the Presidential Commission for the Study of Bioethical Issues 2013 report "*Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts*".

19.10.1 Definitions

Incidental Findings. Results that arise that are outside the original purpose for which a diagnostic test or procedure was conducted.

Anticipated Incidental Findings. Findings that are known to be associated with a test or procedure.

Unanticipated Incidental Findings. Findings that could not have been anticipated given the current state of scientific knowledge.

Secondary Findings. Findings that are actively sought out by a researcher but are not the primary target.

19.10.2 Research Plan

The research plan should contain sufficient information to enable the IRB to evaluate the risks associated with participation in research, the likelihood and significance of risks that can be anticipated, and the adequacy of any steps taken to minimize the likelihood, severity, and impact of those risks.

Investigators should thus include within their research plan that provides information regarding potential for anticipated incidental findings and secondary findings, and a plan to manage such findings, including a plan for validation of results, when appropriate. Likewise, investigators

should include within their plan a process for evaluating and managing unanticipated incidental findings, including consultation with subject matter experts, when appropriate, and the IRB.

The research plan should include specific information about disclosure of incidental and secondary findings, and whether disclosure is planned, the basis for that decision, and, when applicable, the methods for disclosing findings (i.e., inclusion of clinicians and/or genetic counselors in the disclosure discussion, referrals to clinical specialists, etc.).

19.10.3 Consent

The consent process should include a description of the types of incidental findings that might arise including anticipated incidental findings, deliberately sought secondary findings, and the possibility of unanticipated incidental findings. The consent process should also communicate to subjects the plan for disclosing and managing anticipated incidental findings and secondary findings, and whether and how subjects might opt out of receiving such information. This communication is essential to ensure that subjects understand what to expect as a result of their decision to participate in the research; e.g., informed consent.

Despite best efforts to develop, in advance, a comprehensive plan for the management of incidental and secondary findings, VARI recognizes that circumstances do arise that may fall outside of the original plan or that warrant special consideration. For example, a clinically actionable finding significant to the health of a subject arises but the initial plan did not include disclosure of results due to de-identification of samples or another factor.

In these instances, investigators should contact the VARI IRB for guidance and assistance. It should be noted that investigators would likely also be required to coordinate and work with the IRB at the collaborating clinical site in this regard.

19.11 Outreach Activities

As an institution currently focused on basic research involving Epigenetics, Parkinson's Disease and Cancer and Cell Biology, VARI holds annual conferences, symposia and meetings that focus on recent scientific research and invites public participation for some events, including:

- Grand Challenges in Parkinson's disease is a meeting for people with Parkinson's, advocates and caregivers that explores how the Parkinson's community can impact and accelerate research.
- Origins in Cancer is a one-day symposium that brings together students, scientists and medical professionals to discuss the latest breakthroughs in cancer research.
- Han-Mo Koo Memorial Award and Lecture was established to honor the memory and scientific contributions of Dr. Koo whose research focused on genetic targets for anti-cancer drug development for melanoma and pancreatic cancer. Since 2010, awardees have been selected based on scientific achievement and peer recognition. The researchers and the public are invited to the pre-award reception and the Memorial Lecture.

When feedback is solicited from participants, the results are shared with the HRPP Office. As a result, if there is opportunity to make suggestions, these are made to the Symposium planners.

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