UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES

SUBJECT: The Use of Human Subjects in Research at the Uniformed Services University of the Health Sciences (USU)

Instruction 3201

(VPR)

JUL 17 2015

ABSTRACT

This Instruction prescribes Uniformed Services University of the Health Sciences (USU) policies and procedures for the use of human volunteers as research subjects.

A. **Purpose.** This Instruction revises USU Instruction 3201 for protecting the rights and welfare of humans as research subjects.

B. References. *See Enclosure 1.*

C. Applicability. This Instruction applies to the following categories of human subjects research and supports policy and direction provided by the Office of the Under Secretary of Defense for Personnel and Readiness (USD (P&R))

1. Studies conducted:

a. On-campus at USU or in spaces rented or leased by USU.

b. By billeted USU personnel in any location, including on-campus, off-campus at other institutions, in rented or leased spaces, or outside of the United States.

c. In which USU is cited as an affiliated institution.

2. Studies conducted by, or funded through, any foundation or contracted on behalf of USU or USU billeted personnel. This includes studies supported by the Infectious Disease Clinical Research Program (IDCRP).

3. Studies conducted by USU students, residents, and fellows, that:

a. Constitute independent research that may be used to fulfill requirements for a USU academic degree.

b. Are components of a training program conducted at USU or through an academic department or program of USU.

4. Studies in which data are collected at sites other than USU if they:

a. Collect human subjects data via the internet where the data resides on the premises of USU.

b. Advertise and/or solicit on the USU campus for purposes of recruitment of human subjects, including protocols that are not otherwise associated with USU.

5. For the purpose of this Instruction, the F. Edward Hébert School of Medicine (SOM) and Graduate Program, Daniel K. Inouye, Graduate School of Nursing (GSN), Postgraduate Dental College (PDC), Armed Forces Radiobiology Research Institute (AFRRI), USU centers/institutions and all future entities (pursuant to official agreement) are components of USU.

D. Definitions: *See Enclosure 2.*

E. Policies. *See Enclosure 3.*

F. Effective Date. This Instruction is effective immediately.

Charles L. Rice, MD
President

Enclosures:
1. References
2. Definitions
3. Policies
4. Criteria for Exempt or Expedited Review
5. The Use of Human Tissue/Specimens and/or Data in Research
6. Determination of Non-Human Subjects Research Status
7. Emergency Research Consent Waiver under FDA Regulations at 21 CFR 50.24
8. Adverse Events Reporting Policy and Guidelines for Military Research Conducted in the National Capital Region
9. Reporting of Internal or External Adverse Events to the Institutional Review Board (IRB).

REFERENCES

(a) USU Instruction 3201, "The Use of Human Subjects in Research at the Uniformed Services of the Health Sciences," dated July 5, 2011(canceled).

(b) Title 32 Code of Federal Regulations, Part 219, Department of Defense (DoD) Policy, "Protection of Human Subjects."

(c) Title 45, Code of Federal Regulations, Part 46, "Protection of Human Subjects."

(d) Title 21, Code of Federal Regulations, "Food and Drugs," Parts 11, 50, 54, 56, 58,312,314,812.

(e) DoDI 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research," dated November 8, 2011.

(f) Title 50, Unites States Code, Section 1520a "Restrictions On Use of Human Subjects for Testing of Chemical or Biological Agents."

(g) Title 10, United States Code, Section 980, "Limitation On Use of Humans As Experimental Subjects."

(h) USU Instruction, 5501, "Allegations of Scientific Misconduct," dated September 13, 2006.

(i) DoDI 6200.2 Application of Food and Drug Administration (FDA) Rules to Department of Defense Force Health Protection Programs dated February 27, 2008.

(j) Procedures and criteria for the reviews are found in the Implementation of DoDI 1100.13, "DoD Surveys" January 15, 2015.

(k) OMB Directive 15 (October 30, 1997), "Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity."

(1) Section 252 of Public Law 103-160 "National Defense Authorization Act for Fiscal Year 1994," (Public Law 103-160, Sec. 252), November 30, 1993.

(m) Title 42, United States Code, Sections 289g and 289g-2, "Public Health and Welfare."

(n) USU Instruction 5202.1, "Clearance for Public Release of Information and Scientific Materials by Personnel", dated September 13, 2006.

(o) Title 24, United States Code Section 30, "Payments to Donors of Blood of Persons Undergoing Treatment at Government Expense."

(p) 45 Comptroller General Opinions 649, "Personal Services-Private Contract v. Government Personnel-Research Subjects," April 26, 1966.

(q) Title 5, United States Code, Section 2105, 3109, 3371-3376, and 5536.

(r) DoDI 6025.18, "Privacy of Individually Identifiable Health Information in DoD Health Care Programs," dated December 2, 2009.

(s) DoDI 6025.18-R, "DoD Health Information Privacy Regulation," dated January 24, 2003.

(t) Memorandum of Understanding among the Office of the Deputy Assistant Secretary of Defense for Health Affairs (Force Health Protection & Readiness) and the Surgeon General of the Army and the Surgeon General of the Navy and the Surgeon General of the Air Force and The Uniformed Services University of the Health Science, dated January 24, 2008.

(u) 63 Federal Register 60364-60367, November 9, 1998, "Protection of Human Subjects: Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure."

(v) Title 18 United States Code, Section 209, "Salary of Government Officials and Employees Payable Only by United States."

(w) Health Affairs Policy Standards for Off Duty Employment by DoD Healthcare Practitioners http://www.tricare.mil/policy/fy96/offdut50.html.

(x) 5 CFR 2635, "Standards of Ethical Conduct for Employees of the Executive Branch," Subpart H.

(y) Ericka Grimes v. Kennedy Krieger Institute, Inc. 366 Md. 29, 782 A.2d 807 (2000).

(z) Title 5, Code of Federal Regulations, Part 2635.803, "Prior Approval for Outside Employment and Activities."

(a1) Memorandum on "Applicability of Human Research Subject Protections to Certain Activities" from John A. Casciotti, Associate Deputy General Counsel, Health Affairs, dated October 22, 2004.

(a2) Memorandum on "Applicability of 10 U.S.C. 980 to Minimal Risk Research and Research Not Benefiting the Subject" from John A. Casciotti, Associate Deputy General Counsel, Health Affairs, dated October 22, 2004.

(a3) Health Affairs Policy 05-003, "Policy for Protection of Human Subjects in DoD Sponsored Research," dated March 28, 2005.

(a4) Memorandum on the "Department of Defense-wide Human Subject Research Protection Assurances, dated September 7, 2007 from Ellen P. Embrey, Deputy Assistant Secretary of Defense, Force Health Protection and Readiness.

(a5) DoD 5500.7-R, "The Joint Ethics Regulations (JER), including Changes 1-7," dated November 17, 2011.

(a6) Office of the Under Secretary of Defense for Personnel and Readiness, Research Regulatory Oversight Office, "Operating Instruction," dated September 30, 2014.

(a7) Memorandum on the "Minimum Education Requirements for DoD Personnel Involved in Human Subjects Research" dated August 16, 2012, from Patrick A. Mason, Director, Human Performance, Training and Biosystems, Office of the Assistant Secretary of Defense.

(a8) DoD 5400.11-R, "Department of Defense Privacy Program," dated May 14, 2007.

(a9) DoDI 6025.13 "Medical Quality Assurance (MQA) and Clinical Quality Management in the Military Health System (MHS)" USD (P&R) dated October 2, 2013.

(a10) DoD 5141.02, "Director of Operational Test and Evaluation (DOT&E) DA&M, dated February 2, 2009.

(a11) Title 45, Code of Federal Regulations, Part 160 and164, "The Privacy Rule".

DEFINITIONS

Coded Data- (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.

Component Designated Official (CDO)- An office or individual designated by the Office of the Under Secretary of Defense for Personnel and Readiness (USD(P&R)) as USU's institutional oversight authority, in accordance with DoDI 3216.02 (*Reference e*).

Human Subject- Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, OR (2) identifiable private information.

Minimal Risk- Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are no greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Private Information- Information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information or specimens are considered individually identifiable as defined at 32 CFR 219.102(f) (*Reference b*) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Research- Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

POLICIES

USU policies with regard to human research subject protections are set out in Reference (a)- (a-8).

1. Adherence to Human Research Protection Regulations.

a. The regulations adopted by DoD and other Federal agencies for the protection of human research subjects are set forth in *Enclosure* 1 and are followed by USU.

b. USU will maintain a current DoD Assurance certifying compliance with applicable DoD regulations *(Reference a4)*. USU will also maintain a current Department of Health and Human Services (DHHS) Federal Wide Assurance (FWA) certifying compliance with applicable DHHS regulations.

c. USU will accept Assurances issued by DoD or DHHS to an external institution, as long as the external institution's DHHS Assurance clearly states the institution's compliance with human research protections regulations (*References b, c, e and* g). If no DoD assurance is in place, the protocol must be forwarded to the Human Research Protections Official for the Office of the Undersecretary of Defense Personnel & Readiness (OUSD [P&R] Research Regulatory Oversight Office, hereafter referred to as Headquarters) for review. Requirements for compliance with applicable DoD regulations will be verified during the USU protocol review process, which includes Institutional Review Board (IRB) review procedures outlined in this Instruction.

d. Applicable state regulations will also be followed by USU unless instructed otherwise by the Secretary of Defense.

2. USU Human Research Protections Program (HRPP).

a. USU will maintain a HRPP executed through the Office of the Vice President of Research (VPR).

b. The objectives of the HRPP are to:

1) Ensure compliance with applicable Federal and state regulations in the conduct of human subjects research.

2) Ensure that USU investigators, staff, and students receive training in regulatory and ethical standards for the conduct of research.

3) Provide expert consultant services to investigators and students in human research protection.

c. The HRPP Director is a full-time University official and will have appropriate credentials and background in regulatory and ethical aspects of human research. The HRPP Director will:

1) Develop and execute all functions of the HRPP.

2) Supervise the Human Research Protections Program Office (HRPPO) staff, reporting to the Assistant Vice President of Research for all Institutional Review Board (IRB) and HRPP administrative matters.

3) Serve as Executive Secretary of USU's IRBs and assist the IRB Chairs in performing his/her function and report to the USU Institutional Official (IO).

3. Citation.

DoD funded research will generally cite the appropriate section of 32 CFR 219 *(Reference b).* Because institutions outside of DoD commonly Reference 45 CFR 46 *(Reference c),* research funded by non-DoD sources involving institutions outside of DoD may cite the equivalent section(s) of 45 CFR 46 *(Reference c)* or 21 CFR 50, 56,312 and 812 *(Reference d).*

4. DoD Oversight.

a. DoDI 3216.02 *(Reference e),* Section 5.3 requires oversight of human research conducted within DoD by USD (P&R) Research Regulatory Oversight Office, or its designee is the Component Designated Official (CDO).

b. Institutional Official (IO).

The USU President serves as the IO and institutional approval authority. Certain functions of the IO may be delegated. The USU HRPP is executed through the Office of the Vice President, Research (VPR). In compliance with DoD3216.02 Section 5.3 *(Reference e);* USD (P&R), or its designee serves as the Component Designated Official (CDO).

c. Scope. The CDO, in execution of its oversight function, works collaboratively with the HRPPO staff to ensure compliance with DoD 3216.02 *(Reference e)* and other applicable regulations.

d. Oversight Process.

Administrative oversight of the HRPP will be conducted via the following processes:

1) The HRPP Director will ensure that all USU IRB related documents are available to Headquarters via the USU electronic protocol submission system.

2) The HRPP Director will report to the IO, VPR and Headquarters any issues of special concern regarding regulatory compliance or ethical conduct of research. This will

include but not be limited to the following:

a) Any for-cause suspension or termination of an Assurance linked to a USU research project.

b) Any investigation of USU's human research activities conducted by an outside entity.

c) Any investigation of an investigator conducting human research by USU or other Federal entity that results in findings that increase the risk of harm to subjects.

d) Results of routine and for-cause audits of USU's HRPP conducted by regulatory agencies such as the Food and Drug Administration (FDA) and Office for Human Research Protections (OHRP) will be forwarded to CDO within 10 working days of receipt by the HRPP Office.

e) Oversight Authority.

Issues of concern noted in the oversight review requiring PI action or corrective measures will be returned to the USU IRB for further review and action.

5. Resources to Support IRB Review.

As required by Federal Regulations 32 CFR 219, *(Reference b),* the USU President will ensure that there is adequate essential infrastructure to conduct IRB review that includes on-going HRP training, adequate number of qualified and trained personnel assigned to the HRPPO, dedicated meeting space, dedicated office space, and duplication and computing equipment dedicated to the IRB function.

6. Prohibited Categories of Research.

a. Classified research studies. USU will not engage in classified research unless approved by the Secretary of Defense.

b. USU will not engage in research involving prisoners of war, enemy combatants, or detainees of the Federal government.

c. USU will not engage in research involving the testing of chemical or biological agents as described in 50 USC 1520a *(Reference f)* with the exceptions of research for prophylactic, protective, or other peaceful purposes.

d. Very limited exceptions are allowed in 10 USC 980 *(Reference g)* with research in which the informed consent of the subject is not obtained.

7. Scientific Misconduct.

Procedures for handling allegations of scientific misconduct at USU will be processed in accordance with USU Instruction 5501, "Allegations of Scientific Misconduct" *(Reference h).*

8. Non-compliance with this Instruction.

Incidences of non-compliance with this Instruction will be promptly investigated by the HRPP Director under the direction of the IRB Chairs and referred to the IRB and appropriate institutional Officials for action.

9. Activities Not Covered by this Instruction.

a. Use of investigational new drugs, biological products, or devices for purposes of force health protection governed by DoD 6200.2 *(Reference i)*.

b. Accepted medical practice undertaken for purposes of treatment, is not research and thus not subject to DoDI 3216.02 (*Reference e*) or this Instruction.

c. Activities that do not meet the definition of human subjects research in accordance with the applicable DoD and DHHS policy. Criteria are addressed in Enclosure 6.

10. Review of Protocols

a. General.

The USU IRB and the USU IO or designee, will approve all USU research studies involving human subjects before enrollment can begin. The IO may delegate final approval authority to the IRB Chairs for all but initial approvals. For studies that involve external institutions, approval from the comparable human subjects protections review committee of the external institution will also be obtained. These may include a DoD Military Treatment Facility (MTF), or other U.S. Government health care facilities, as well as civilian institutions including hospitals, universities, commercial entities, and research institutes. For each study, either USU or an external institution may serve as the lead IRB and/or with appropriate authorization, may serve as the IRB of record with primary oversight responsibility for the research.

b. Review of Human Subjects Research at USU.

In order for a protocol to be reviewed by the USU IRB, the Principal Investigator (PI) must be a USU billeted or assigned personnel, USU student, or contractor personnel at USU with PI eligibility.

c. Studies for which USU is the IRB of record or the designated central IRB for multisite studies.

PI's will submit their human research protocols to the USU IRB if the study is located at USU and/or any sites or institutions for which USU has direct Human Research Protections oversight responsibility. For sponsored-projects that have been submitted to the Office of Sponsored Programs (OSP), the OSP designator should be referenced on the IRB study protocol. For intramural protocols, the Office of Program Development (OPD)

designator should be referenced on the study protocol.

d. Administrative Review of External Studies covered by this Instruction.

This applies to instances where USU is not a performance site but is providing material support to the study (*e.g.,* funding, facilities, equipment, personnel, access to or information about DoD personnel for recruitment, or identifiable information or specimens from living individuals). All human subjects research protocols involving USU must be submitted for review and approval by an IRB, as applicable. In cases where USU personnel are engaged in a human research study conducted at another institution, a DoD Institutional Agreement for IRB Review (IAIR) will be applied on a case-by-case basis. Determination of the responsible IRB is based on location of the subject/patient population, funding, PI's affiliation, and other decisional factors. The decision will be made collaboratively by the Human Protections Administrators (HPA) at USU and the external Institution.

An Administrative Review *(Reference a6)* is conducted by designated HRPP staff of studies reviewed and approved by a DoD IRB for the purpose of ensuring that all required documents are included in the study package. This is a "paperwork check" that includes a review of the primary IRB's determination memorandum, the totality of documents submitted to the primary DoD IRB for review. An acceptance memorandum by the Human Research Protection Official (HRPO) will be made to formally acknowledge the review.

e. Studies from the Infectious Disease Clinical Research Program (IDCRP) *(Reference t).*

The Infectious Disease Central IRB (IDIRB) is administratively supported by the University's HRPP office. Each DoD Service component is represented in the IRB membership roster and these members may come from the University, the clinical research network of Medical Centers, and non-affiliated Federal institutions. The ID IRB is comprised of members representing institutions participating in the IDCRP. In an agreement between the University and the Services, Headquarters Level Administrative Review of University ID IRB protocols will remain at USD (P&R) but will be supplemented by a representative from each Service.

f. HRPO Reviews - Reviews conducted by designated HRPP staff members to ensure that protocols adequately address and fully comply with DoD-specific requirements for the protection of human subjects, as stated in DoDI 3216.02 *(Reference e)* when studies are initially approved by a non-DoD IRB. These reviews are required when (i) the collaborating non-DoD institution has an appropriate Federal Assurance; (ii) DoD involvement is secondary to that of the non-DoD institution; (iii) a written agreement between the two institutions is in place (*e.g.,* an IAIR). The designated HRPO may "accept", "concur", "non-concur" or "concur with modifications required in order to comply with DoD-specific requirements." *(Reference a6)*

g. Reconciliation of IRB stipulations in multi-site protocols.

Changes to the protocol required by other IRBs in a multi-site study in which the overall PI is billeted at USU, must be submitted to the USU IRB for review and approval. The informed consent document may be modified to meet local requirements.

h. Approval Authority.

No research involving human subjects may be conducted until the PI receives written notification of USU IRB approval. The IO or designee is the final institutional authority who will approve research that was reviewed and approved by the IRB. Certification of institutional approval occurs with approval by the IO. The following apply:

1) The USU President or IO designee may not approve human subjects research if it has not been approved by the USU IRB.

2) The USU President or IO designee may not approve human subjects research that has been disapproved by the USU IRB.

3) The USU President or IO designee may disapprove a protocol or may require changes to a protocol approved by the IRB as a condition of final approval. In the latter instance, the protocol may be returned to the IRB for review or may be returned to the PI for revisions and subsequent IRB review.

i. Study Criteria.

1) Definition of human subject and research. See DEFINITIONS *(Enclosure 2)*.

2) General.

The IRB will examine proposed studies to determine whether DoD, DHHS, and other regulatory requirements for the approval of research are met. These criteria include the following:

a) Risks to subjects are minimized.

b) Potential benefits to subjects will be maximized.

c) Risks to subjects are reasonable in relation to anticipated benefits.

d) Selection of subjects is equitable, to include subject recruitment procedures.

e) Unless waived, consistent with 10 USC 980 *(Reference g)*, written informed consent is sought from each prospective subject or the subject's legally authorized representative and appropriately documented.

f) Where appropriate, the research plan makes adequate provision for monitoring data that are collected to ensure safety of subjects.

g) Where appropriate, the research plan makes adequate provision for protecting the privacy of subjects and subjects' family, and maintaining confidentiality of the data.

3) Double-Blind Studies/Use of Placebos/Deception.

A protocol with an experimental design that involves the use of double-blind

procedures, placebos, deception or less than full disclosure will be fully explained in the protocol and the consent process will be given explicit IRB approval.

4) Debriefing of Subjects in Studies Involving Less than Full Disclosure.

Subjects will be debriefed after participating in a study involving less than full disclosure or deception. Debriefing will concentrate on the nature of the subject's participation and the results obtained. Debriefing may be omitted if the procedure is risk free, or if the IRB finds it is not in the subject's best interest. Whether deception is necessary and acceptable and what safeguards, if any, are necessary will be determined by the IRB during the review process.

5) Studies Using Hospitalized Patients.

Studies involving hospitalized patients or studies requiring in-hospital testing or care of subjects will be conducted at a DoD MTF or other United States government hospital on beneficiaries who are eligible for admission to these hospitals. In cases where research subjects are anticipated to complete their service or deployment resulting in the loss of health care benefits while participating in research, permission from the local MTF command must be obtained prior to subject enrollment. Extending health care benefits in such cases will ensure that subjects, who are no longer DEERs eligible, receive care if complications related to study participation will require treatment or hospitalization.

When studies are proposed for non-government hospitals, approval may be granted if the IRB is satisfied that subject's rights are adequately protected, and if the President or designee, USU, approves the use of the non-government hospital.

6) Location of Clinical Research.

All research involving physical intervention of human subjects will generally be conducted in an approved MTF. The committee, or the Chairs acting on behalf of the IRB, may determine that the physical intervention is such that it may be conducted outside an MTF. Physical intervention includes for example: drawing blood, treadmill testing, and giving injections. It does not include administering pen and pencil tests or conducting class exercises.

j. Research Monitor Policy.

1) General.

DoD 3216.02 *(Reference e)* requires that an independent Research Monitor be appointed by name if the IRB determines that the research risk is more than minimal. Research Monitors may also be appointed for minimal risk protocols if deemed appropriate by the IRB. Research Monitors will be appropriately qualified individuals capable of overseeing the progress of research protocols, especially issues of individual subject management and safety. Research Monitors will be independent of the investigative team and possess sufficient educational and professional experience to serve as the subject advocate.

A copy of the Research Monitor's applicable license and a summary of the monitor's duties, authorities, and responsibilities will be submitted with the study protocol for IRB review and approval.

2) Duties of the Research Monitor.
The designated Research Monitor will:

a) Complete human subjects training at the level required of principal investigators.

b) Be thoroughly familiar with the research protocol and review research progress with the PI at intervals that are appropriate given the study design.

c) Review and consult on individual cases and evaluate adverse event reports.

d) Report discrepancies or problems to the IRB via the HRPP Director or IRB Chairs.

e) Take whatever steps are necessary to protect the safety and well-being of research subjects. Research Monitors may independently stop a research activity in progress, remove individual subjects from a study, or modify study procedures to address problems and decrease subject risk until the IRB can assess the Research Monitor's report.

f) Depending on the nature of the study, assess one or more of the following phases of a research project: subject recruitment, subject enrollment, data collection, and/or data storage and analysis.

g) Avoid potential conflicts of interest that may impede objectivity in the assessment of study risk. For example, Research Monitors may not serve in roles on a study other than the Research Monitor role, nor serve as authors on scientific manuscripts or presentations resulting from the study, nor be in a situation in which they may be subject to influence due to financial, professional, or other interests.

h) Assist in auditing the study files during the continuing review.

i) Immediately inform the HRPP Director or IRB Chairs if they become unable to perform the duties of Research Monitor for the study.

k. Defense Manpower Data Center (DMDC) Report Control Symbol (RCS) Review.
Research involving attitude and opinion surveys of individuals that require participation of personnel from more than one DoD Component or personnel from DoD Component(s) other than the sponsoring DoD Component must be reviewed and recommended for approval or disapproval to the Director, Washington Headquarters Services by the Defense Manpower Data Center's Human Resources and Strategic Assessment Program. The purpose of this review is to

ensure compliance with the Office of Management and Budget guidance on Federal surveys. When applicable, this review fulfills the scientific review requirement. *(Reference a6)*

Procedures and criteria for the reviews are found in the Implementation of DoDI 1100.13, "Surveys of DoD Personnel" *(Reference j)*.

11. Protocol Requirements.

1) General Protocol Format.

a. All protocols will be completed in accordance with *(Reference b)*. All human research protocols will be submitted to the IRB on the IRB Protocol Application Form. The acceptable IRB Protocol Application Form is located on the University's electronic IRB protocol submission site.

b. If an interview or questionnaire is used in the study, a copy will be appended to the protocol.

c. The proposed consent form(s) will be attached. A description of how and by whom the informed consent is obtained will be included.

d. Data collection tools, case report forms, Curriculum Vitae (CV), Researcher Responsibility forms and Conflict of Interest forms, Clinical Investigator's Brochure (IB) or product inserts, if applicable, coversheet, human subjects protections training certifications, approved contract or funded grant, FDA Form 1572 (for investigational new drug studies), and current provider licenses (for FDA regulated and National Institutes of Health funded studies) also will be submitted.

e. Protocols should contain detailed explanations of subject exclusion and inclusion criteria.

f. Data collection that includes demographics of race and ethnicity will comply with OMB Directive 15 (as revised on October 30, 1997) *(Reference k)*.

g. It is expected that women and minorities will be included per DHHS or DoD guidelines unless there is adequate justification for exclusion. Women will not be excluded due to gender from studies oriented toward operational situations or roles. The selection of subjects reflecting gender and minority participation as appropriate shall comply with Section 252 of Public Law103-160 *(Reference l)*. The Head of DoD Component may exercise the waiver authority under this law *(Reference e)*.

2) Additional items to be provided as applicable:

a. If other IRBs have reviewed the study, their determinations (e.g., pending, approved, or disapproved) will be provided to the IRB by the PI or by the review board(s).

b. When a study seeks the participation of a vulnerable population, such as military personnel, children, prisoners, mentally impaired or economically disadvantaged, the protocol must be compliant with DoDI 3216.02 *(Reference e)* and should contain justification for their use and state specific protections if such are available. In addition, if research is being conducted in Maryland, a parent, appropriate relative, or other applicable surrogate, cannot consent to the participation of a child or other person under legal disability in greater than minimal risk research without direct benefit to the subject or studies in which there is any risk of injury or damage to the health of the subject. *(Reference y)*.

c. When a study will be carried out within a particular racial, religious, or geographic community, the IRB may require the PI to explain the nature and extent of any preliminary contacts with community representatives to determine acceptance of the study by the community. If the study will be conducted within a school, business, or other institution that does not have an IRB, the PI will outline any preliminary contacts with and provide documentation of permission from the appropriate officials. If possible, this will be documented by correspondence with the community representatives or officials.

d. When a new drug, an old drug, or device will be used outside of the FDA-approved indication for research purposes, the PI will provide documentation of the filing of the appropriate forms and information with the FDA or that the FDA has waived jurisdiction for the specific study.

e. Fetal tissue research supported or conducted by DoD shall comply with 42 USC 289g-289g-2 *(Reference m)*.

f. Research involving stem cells will be reviewed for compliance with current regulations.

12. Reports and Records

a. Continuing Review Reports.

Continuation reports for each IRB approved project will be submitted to the IRB Office no less than annually or sooner as determined by the IRB, using the appropriate IRB forms located on the University's electronic protocol submission site. For those projects requiring reports more than annually, these reports will be submitted as requested by the IRB.

b. Final Reports.

A final human research report following completion or termination of the non-exempt research project will be submitted to the IRB for each approved protocol within 90 days of the completion of the study.

c. FDA Reporting.

USU requires that PI's using investigational drugs or devices comply with all FDA requirements. A copy of the IND/IDE application, letters and/or memos to the FDA will be provided to the IRB.

d. Reports to industry sponsors.

The PI is responsible for submitting the appropriate reports to the sponsoring drug or device company, as specified in the research agreement, as applicable.

e. Adverse Event Reports.

See *Enclosure* 7, "Adverse Event Reporting Policy and Guidelines for Military Research Conducted in the National Capital Region."

f. Waiver of Enrollment Criteria

For more than minimal risk studies, all waivers of inclusion/exclusion criteria must be prospectively approved by the IRB. For FDA regulated products, a waiver or exception to the protocol inclusion/exclusion criteria may be used in emergency/ life-threatening situations where there is no satisfactory alternative therapy available and there is insufficient time to apply for IRB and FDA approval of the waiver. This mechanism allows a patient to receive the investigational drug/device even if one or more of the protocol entry criteria has not been met. The authorization to ship and use the drug may be given by the FDA official over the telephone or other rapid means of communication. The PI must comply with FDA requirements and submit a full report to the IRB, FDA and the sponsor within five working days of administering the investigational product. Concurrence by an uninvolved physician and approval from the sponsor must be obtained and the ICD for the ongoing trial may be used but patients must be informed that they are not research participants.

g. Maintenance of Research Records.

1) The following will be filed in the subject's record: a copy of the signed consent form; documentation or code identifying any drugs administered, investigational or not; investigational procedures performed; significant observations, including effects, physical, and mental state of the subject; and tests and laboratory procedures performed. The record may contain any additional material the PI believes is relevant.

2) The PI will retain all research records for ten (10) years (*Reference a6*) and the period governing retention of medical records in the jurisdiction (state or county) where the research is conducted (generally to the age of 18 plus 10 years for minors, and 10 years for adults).

In the event that the PI departs the University during this period, the PI's Department Chair or equivalent unit head will assume responsibility for retention of records.

3) For all research records pertaining to clinical trials of a compound to be considered for FDA approval, the FDA regulations will be followed *(Reference d)*.

4) PI's are required to keep a copy of the approved protocol, modifications, all approval letters, any protocol related correspondence between the PI and the IRB, and any other documents in connection with the research project.

13. Human Research Protections (HRP) Training.

a. Human subject protections training must be certified, according to current policy, for all personnel involved in the conduct, review, or approval of human subjects research *(Reference a7)*. HRP certification includes training on the Nuremberg Code, the Belmont Report, 32 CFR 219 (45 CFR Part 46), DoDI 3216.02 and this Instruction.

b. All personnel listed as members of the research staff or collaborators on a USU research protocol must complete the required HRP training. In the event that the HRP training certification of any member of the research staff expires, the PI must ensure that the HRP training for that staff member is completed prior to engaging in any human research activity.

c. The OUSD (P&R) requires training at the following levels: *(Reference a6)*.

1) Personnel involved in research oversight, including institutional officials, IRB members, and IRB staff.

2) Investigators and scientific staff who conduct human subjects research, Research Monitors assigned to human subjects protocols.

3) Staff members who assist in the conduct of human subjects research or have access to identifiable human subjects data as a member of the research team.

d. Personnel with access to Protected Health Information (PHI) for research purposes, as defined in DoD 6025.18-R *(Reference r)* will complete HIPAA training.

e. Laboratory or technical support service providers who are not engaged in human subjects research are not required to complete human subjects training. Examples of personnel in this category would include technicians who analyze coded samples or technicians who provide services (for example, an MRI scan or blood draw) at an external facility.

14. Manuscript Clearance.

USU procedures for manuscript clearance are defined in USU Instruction 5202.1, "Clearance for Public Release of Information and Scientific Materials by USU Personnel," *(Reference n)*. Manuscript clearance is generally conducted by the Department Chairs and the USU Office of External Affairs.

15. Recruitment of Research Subjects.

a. Contacting Subjects.

The investigator will contact subjects in a way that will not embarrass or inconvenience them or otherwise intrude on their privacy. If the study involves patients, the patient's physician or other health care provider will be informed or consulted before the investigator contacts the patient.

b. Requirements Regarding Advertisements, Commercials, Flyers, etc. for On-Campus Subject Recruitment.

1) Before recruitment of human subjects is permitted on campus, the USU IRB will review and approve the study and advertisement. This review may be by the convened IRB or through an administrative review by the IRB Chairs or designee, as appropriate. If approved via administrative review, the convened IRB will be informed of the approval at the next convened meeting. Recruitment materials (radio, print advertisements, etc.) should not include the amount of compensation for participants in the study. Advertisements without a USU IRB stamp of approval will be removed from USU property.

2) Only the IO may approve requests from external Investigators who wish to recruit research subjects on-campus. The request must state that they will comply with the USU human research protections policies and submit the request to the HRPP Director. A subcommittee of the IRB will conduct an initial review of the recruitment request and coordinate with the Office of External Affairs. The subcommittee has the authority to deny the request or move it forward for IRB review. The IRB's role is to recommend approval by the IO.

c. Recruitment of Uniformed Students and other Uniformed Personnel.

1) Recruitment must be in accordance with DoDI 3216.02 *(Reference e)*. No investigator, regardless of his/her service affiliation, is permitted to use mandatory military assemblies or formations to inform or recruit students for a human subject use protocol. Use of academic (classroom) settings is discouraged. If recruitment in a classroom or a similar group setting is necessary, recruitment processes must not subject students to coercion or influence through the hierarchical command structure of the military.

2) Recruitment will be divided into two separate and distinct phases:

a) Phase 1: An informational briefing in which the purpose(s), methods, risks, benefits, issues of confidentiality, time commitment, and other pertinent issues regarding the specific research project and human subjects are discussed.

b) Phase 2: An enrollment session in which human subjects agree to participate by reading, signing, and ensuring understanding of an informed consent document.

3) Unit officers and senior noncommissioned officers (NCOs) in the chain of command shall not be present during research subject enrollment sessions in which members of units under their command are afforded the opportunity to participate as research subjects.

Officers and NCOs so excluded shall be afforded the opportunity to participate as research subjects in a separate enrollment session.

4) Civilian or military faculty who exercise authority over or influence grades, class standing, or future assignments of students should not be present during enrollment sessions for students. However, this requirement may be waived by the IRB.

5) At all recruitment sessions, including informational briefings and enrollment, an ombudsman not connected in any way with the proposed research shall be present to monitor and ensure that the voluntary nature of participation is applied and that the information provided about the research is adequate and accurate.

6) Following any informational briefing, there must be time allowed for questions from potential participants when officers and NCOs in the chain-of-command and faculty are not present. If the investigator is within the chain-of-command and/or a faculty member, then that officer or faculty member may stay to answer general questions, but must exit the meeting after the question- and- answer session to allow students to ask specific questions of an individual who is not in a position of authority over them. In these cases, the investigator may wait outside the room to serve as a resource person and allow another person who is knowledgeable about the protocol to remain in the room specifically to answer questions.

7) Sufficient time must be given between the informational briefing and enrollment session to allow students to thoughtfully consider their participation.

8) The above procedures do not preclude students from volunteering for a study in which one of their professors is an investigator. A concern this possibility raises is that students could be influenced by this awareness. The USU IRB should evaluate this concern carefully if it is germane to a protocol that it is reviewing.

9) The recruitment of uniformed student subjects entails special requirements detailed below (see section 19. "Special Categories of Review: a. Uniformed Medical and Nursing Students")

d. Non-Uniformed Students as Subjects.

Procedures for recruitment of non- uniformed students must not be coercive or suggest preferential treatment.

e. USU Employees as Subjects.

Federal employees are required to follow their Command/Agency's policies in obtaining approval prior to participation in a research study. When civilian or uniformed employees of the Federal government volunteer to participate in human subject research studies, the following provisions will apply:

1) Employees must have the approval of their immediate supervisor to participate during duty time. Documentation of approval should be provided to the PI or to a member of the

research team prior to participation and acceptance of payment in connection with the research study.

2) Participation outside an employee's regularly scheduled duty or during leave is not considered duty time. If compensated, the employee must take leave or participate in the study during off-duty time. Off-duty employment qualifications must be followed. The employee will be informed of the above *(References z and a5)*.

3) Solicitation and selection of employees must not be coercive or suggest preferential treatment.

4) Generally, investigators will not use employees under their supervision as research subjects. However, if an employee wishes to participate in his or her supervisor's study, the employee may seek the approval of the IRB. A special form ("Employees as Research Subjects") is available from the IRB Office that must be completed by the employee before his/her participation in the study.

5) "Compensation of Federal Employees Participating in Research." See section 16 below for compensation standards.

f. Retired Military and Beneficiaries Subjects.

Retired military personnel, beneficiaries, and others entitled to medical care in military facilities may participate as human research subjects and may be compensated as authorized by applicable directive *(Reference p and q)*.

16. Compensation of Federal Employees Participating as Subjects in Research.

Compensation to human subjects for participation in research will follow DoDI 3216.02 *(Reference e)*.

a. Federal subjects paid directly from a Federal source.

1) During working hours for which they are being compensated by the Federal government, uniformed and civilian Federal employees may not be paid by another Federal source or by an outside party *(Reference v)*. One exception to this rule is that Federal employees (civilian and uniformed) participating during working hours may be compensated from a Federal or non-Federal source up to $50.00 for a blood draw if the research meets the purposes of 24 USC 30 *(Reference o)*. For all other compensations, the Federal employee (civilian or uniformed) must be in a non-duty status. They may participate with appropriate supervisory approval without compensation during duty hours. The duty day for medical students and graduate nursing students is determined by the Commandant of the F. Edward Hébert School of Medicine (SOM) and Graduate Program and the Commandant of the Daniel K. Inouye Graduate School of Nursing (GSN) (respectively).

2) DoD graduate students and medical residents are prohibited from engaging in off-duty employment and therefore may not be compensated for their participation in research *(Reference w)*.

3) During non-duty hours, Federal employees (civilian and uniformed) may be compensated for participation in research studies, only after they have received appropriate approval in accordance with their agency/command requirements. Many agencies/commands require these requests to be reviewed by a standards of conduct official in addition to reviewing them for potential impact on readiness *(Reference x).* If payment is made from a Federal source to DoD active duty personnel, payment is restricted to up to $50 per blood draw *(Reference o).* The institution may develop a local form to assist the participant in obtaining approval; however, it is up to the discretion of the employee's agency/command whether this is sufficient to meet their local requirements.

b. Non-Federal Monies Used for Compensation.

1) Cooperative and other studies that may involve non-Federal participation and funding change the dynamics of compensation in that previously stated dollar limitations do not apply. However, Federal employees are still required to obtain authorization to engage in off-duty employment as outlined in a.3 above *(Reference x).*

c. Amount of Compensation Allowed.

1) It is the responsibility of the IRB to examine the amount of compensation provided to ensure there is not an "undue inducement" to participate in research. *(References b and c).* Determinations will be made on a study-by- study basis.

17. Informed Consent Requirements.

An Informed Consent Document (ICD) is required that includes the basic elements of consent as specified in *(References b, c and d).* For IDCRP ICD(s), forms are to be submitted using the local sites templates.

a. Consent to participate in a USU study will only be obtained from a competent person or that person's legally authorized representative and will meet the requirement set forth in DoD and DHHS regulations. *(Reference b, c, d and g).*

b. The investigator will document the consent process by assuring that:

1) The consent is obtained using the current, approved ICD.

2) The ICD is signed on the last page by the subject, and the research team member who explained the study procedures to the subject. If the IRB finds it necessary to have a witness to the consent process or a witness is otherwise required by law or regulation, the IRB will specify the scope of the witness requirement and this should be outlined in the witness signature block of the ICD as evidence that the witness requirement and scope was understood and complied with. The PI shall ensure that informed consent documentation is properly completed. The IRB may require the subject's initials on each page of the ICD if it deems it necessary.

3) The signed ICD is filed and maintained in accordance with the provisions on

Maintenance of Research Records *(see section 12(g) of this Instruction).*

4) A copy of the signed ICD is provided to the subject.

c. Consent documents will not contain exculpatory language in which the subject waives, or appears to waive, any of his or her legal rights, including any release of USU from liability.

d. When new information becomes available that could possibly affect or increase the risk to subjects related to participation in the study, the PI must modify the ICD to include a statement of new findings and submit it for IRB approval. In addition, subjects currently on active protocol interventions must be re-consented with the updated ICD.

e. Written consent may be waived or modified under special circumstances. The IRB will follow the procedures set forth in *(References b through e)* when it waives the requirement for written informed consent, or approves a procedure that does not include or alters some or all of the elements of informed consent.

f. Use of a Validated ICD.

The approved ICD will have the IRB certification of approval and the expiration date visible. The current version of the certified approved ICD is the only version authorized to be used to consent subjects.

18. Informed Consent: Special Circumstances.

a. DoD requirements under 10 USC 980 *(Reference g).* Appropriated funds may not be used for research involving a human being as an experimental subject unless:

1) The informed consent of the subject is obtained in advance.

2) In the case of research intended to be beneficial to the subject, if the subject lacks capacity due to age, condition, or other reason, to make a decision regarding consent to participate in the research, prior informed consent may be provided by a legally authorized representative of the subject. In any such case, the determination that research is intended to be beneficial to the subject must be made by the IRB *(Reference g).*

b. Consistent with *(Reference g),* the requirement for prior informed consent may be waived by the Secretary of Defense or designee with respect to a specific research project for national defense purposes and/or to advance the development of a medical product necessary to the Armed Forces, if the research project may directly benefit the subject and is carried out in accordance with all other applicable laws and regulations, including 21 CFR 50.24 *(Reference d).* For research that has been determined by the IRB to be "minimal risk," the indispensable and unalterable elements of informed consent are that participation is voluntary for the subject and the subject understands the risks. Therefore, in the context of research risks comparable to those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests, if those routine risks are understood by the subject and participation is completely voluntary, a process that the IRB approves as compliant with 32 CFR 219.116 *(Reference b)* would comply with the informed consent mandate and would not violate 10 USC 980 *(Reference g).*

c. Consent Waiver for Planned Emergency Research. Procedures for this exemption are defined below in emergency research consent waiver under FDA regulations at 21 CFR 50.24 *(Reference d).*

19. Special Categories of Review.

a. Uniformed Medical and Nursing Students.

1) General Policy.

The USU IRB will review and provide a recommendation to the appropriate Commandant and Dean as to the acceptability of USU uniformed medical and nursing students to serve as research subjects.

2) Recommendation for approval of uniformed medical and nursing student participation will be based upon a number of factors including evaluation of benefits versus risks, the time and effort required of students for participation, and potential distraction or conflicts with the educational and military objectives of uniformed medical and nursing students enrolled at USU *(Reference e).*

b. Approval Process for Uniformed Medical and Nursing Student Research Participation.

1) Uniformed medical and nursing students may participate as human subjects in research being conducted at USU or at any other institution only if the following approvals are obtained, in the sequence indicated:

a) The research protocol has been approved by the USU IRB. A copy of the approved protocol, consent form and IRB approval memorandum will be forwarded by the PI to the appropriate Commandant and Dean for review.

b) There is concurrence of the USU IRB recommendation by the Commandant, SOM or the Commandant, GSN, as appropriate.

c) There is concurrence of the USU IRB recommendation by the Dean, SOM or the Dean, GSN, as appropriate. Upon approval by the appropriate Dean(s), the study may be executed.

d) Concurrences by the appropriate Commandant and Dean are provided to the IRB Office.

e) Final approval is by the Institutional Official or designee, USU, who serves as approval authority for USU on all matters regarding the protection of human subjects.

f) A Commandant or Dean may request or conduct a "pre-review" of a protocol involving uniformed medical and nursing students and indicate stipulations that will be a

prerequisite for their final approval. The appropriate Commandant and Dean will review the IRB approved version of the protocol when the review process is complete.

g) Active duty military personnel who participate as human subjects generally may not be compensated for participation while in active status. See Section 16,"Compensation of Federal Employees Participating in Research" of this enclosure for compensation standards. In the case of USU military personnel, this approval must be obtained from the member's commanding officer.

20. Privacy Rule.

Personally identifiable information (PII) as defined under DoD 5400.11-R (*Reference a8*) and collected within the organization must be protected. The use of PII is under the oversight of DoD Privacy Program. The University Privacy Office (housed under the Office of Accreditation and Organizational Assessment (OAC)) is available for consultation or support to any IRB reviews within the context of the Privacy Program.

Health Information collected within an organization defined as a covered entity under the Health Insurance Portability and Accountability Act (HIPAA) of 1996, may be classified as Protected Health Information (PHI). Note that PHI is a subset of PII. Special protections are required for research studies that use or disclose PHI. The PI and all members of the research staff are responsible for compliance with HIPAA requirements *(Reference a11)* as applicable. Should the PI depart USU, the PI's academic department will assume responsibility for the protection of PHI associated with the research project.

Information Defined as PHI under HIPAA.

There are 18 categories of direct identifiers that are considered PHI when associated with health information. These are listed in Table 1.

TABLE 1: Categories of identifiers defined as Protected Health Information (PHI)

1) Names

2) All geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code 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) Fax numbers.
6) Electronic mail addresses.
7) Social security numbers.
8) Medical record numbers.
9) Health plan beneficiary numbers.
10) Account numbers.
11) Certificate or 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 finger and voice prints.
17) Full-face photographic images and any comparable images.
18) Any other unique identifying number, characteristic, or code.

b. Criteria for De-Identified PHI.

The HIPAA standard for de-identified or anonymous datasets is removal of all 18 categories of PHI defined above.

c. Limited Datasets (LDS) under HIPAA.

A limited dataset allows the use of dates, age, addresses no smaller than a zip code and other numbers, characteristics or codes not listed as a direct identifier. A LDS for research purposes requires a Data Use Agreement (DUA). A DUA is enacted between a covered entity and the recipient of PHI.

d. USU review of studies involving PHI.

1) The USU IRB may serve as a privacy board to ensure compliance with HIPAA regulations by USU personnel.

2) In reviewing protocols involving PHI, USU will ensure that the appropriate research subject authorization or data use agreements are in place to permit the use and disclosure of PHI as research data.

e. Protocol requirements.

1) Protocols that involve the use and disclosure of PHI will include a HIPAA compliant Research Subject Authorization (RSA) form, which will be included as part of the consenting process. A RSA form may be incorporated into a compound ICD in connection with a specific research protocol.

2) Protocols that propose to use and disclose PHI addressed through an institutionally

approved waiver or data use agreement with a covered entity will include copies of all relevant documentation as part of the USU protocol submission.

f. Requirements for HIPAA research subject authorization forms.

1) A valid authorization must contain, at least, the following core elements:

a) A description of the PHI to be used and /or disclosed.

b) The identity of the individual(s) or organizations who may disclose PHI and the identity of the person or organization to whom PHI may be disclosed, including disclosure to DoD representatives and/or the Research Monitor.

c) The purpose of the requested use or disclosure.

d) An expiration date or an expiration event that describes the conclusion of the use or disclosure. The statement "end of research study," "none," or similar language is sufficient if the authorization is for use or disclosure of PHI for research, including for the creation and maintenance of a research data or research repository.

e) Signature block of the subject and date signed.

2) Research Subject Authorization Form Required Statements. In addition to core elements, the authorization must contain statements adequate to inform the subject of the following:

a) The individual's right to revoke the authorization in writing, any exceptions to the right to revoke authorization, and a description of how the individual may revoke the authorization.

b) A statement that the covered entity may not condition treatment, payment, enrollment or eligibility for benefits on whether the individual signs the authorization.

c) A description of any potential for PHI disclosed pursuant to the authorization to be subject to redisclosure by the recipient, including any scenario in which the PHI would no longer be protected by the Privacy Rule (for example, disclosure to parties outside of U.S. legal jurisdiction).

3) Other Authorization Form Requirements.

a) The authorization must be written in plain language.

b) The subject must be given a copy of the signed authorization.

g. Operating Procedure for use of PHI.

USU protocols that involve the use and disclosure of PHI should include operating

procedures for handling PHI compliant with DoD 6025.18-R *(Reference r)* which must include the following sections:

1) Background: Provide a brief description of the purpose and objectives of study, including the rationale for inclusion of PHI.

2) Categories of PHI Used: Describe the exact categories of PHI used in the study.

3) Data Handling and Security
Procedures: Include the language and information described below: "The following procedures and physical security measures will be followed to ensure compliance with HIPAA standards as defined in DoD 6025.18-R *(Reference r)*.

a) PHI requested by the PI at USU is the minimum necessary for the stated purpose of the analysis and will be used only for the time period set forth in protocol [protocol number] approved by the USU IRB on [date].

b) PHI will not be used or further disclosed for any purpose.

c) Appropriate safeguards will be used to ensure proper use of PHI through the following measures:

(1) Electronic PHI data must be encrypted. The method of transfer of data sets containing PHI between sites must be described in the protocol and must be reviewed and approved by the Privacy Board/IRB.

(2) A copy of each data set transferred to or from USU will be stored in a secure manner as a Reference. A record of the data transfer must be maintained in a tracking log by the PI so that a complete audit trail exists for all data transfers that involve PHI.

(3) The tracking log will include the following: Date of transfer; data source (institution and POC); USU data recipient (name and contact information); transfer method; storage media; PHI description; sample size.

d) Only authorized Individuals may have access to protocol-related PII/PHI.
Actual or possible loss of control (lost, stolen, or compromised information), means an unauthorized disclosure, or unauthorized access of personally identifiable information where persons other than authorized users gain access or potential access to such information for an "other than authorized purposes" where one or more individuals will be adversely affected. Such incidents also are known as breaches of confidentiality.

Any instance of potentially lost, stolen, or compromised PII/PHI and/or non-compliance with privacy regulations/protections must be reported to the HRPP Director and

USU Privacy Office immediately to ascertain, by an investigation, if a potential or actual breach has occurred that must be reported within 24 hours to the United States Computer Emergency Readiness Team (US-CERT) and the Office of the Secretary of Defense/Joint Staff Privacy Office immediately.

21. Genetic Research Policy

a. General.

Considerations of genetic research involves a higher level of scrutiny when risks extends to an individual's as well as family members' genetic tests, genetic tests of any fetus of an individual or family member who is a pregnant woman, and genetic tests of any embryo legally held by an individual or family member utilizing assisted reproductive technology. Risks associated with genetic information also includes the manifestation of a disease or disorder in an individual's family members (family history); or any request for, or receipt of, genetic services or participation in clinical research that includes genetic services by an individual or an individual's family members.

b. Guidelines.

In general, subjects donating tissue/specimens to be used in genetic research will be informed about the purpose(s) of the study, specimen storage, if and when, or whether they will or will not receive study results, plans to handle incidental findings (e.g., paternity, disease conditions other than what may be under study), plans for future use and re-contact, and risks (e.g., insurability, employability, paternity suits, reproduction, social stigmatization, etc.). Subjects will also be informed of measures to protect their confidentiality, any related monetary costs (e.g., genetic and/or psychological counseling), options for study (and specimen) withdrawal, and commercial interests and financial benefit (if any) from that interest.

22. FDA regulated Investigational New Drug (IND) and Investigational Device Exemption (IDE) Protocols.

a. Protocols involving an investigational new drug or device will comply with FDA regulatory and Good Clinical Practice (GCP) requirements.

b. The PI's IRB application will address the 30-day interval in which the FDA gives the approval for the study to proceed *(Reference d)* or whether the FDA has waived the requirement for an IND or IDE application. If the 30-day interval has expired and a waiver has not been received, the PI will contact the FDA to inquire about the status of the application.

c. The IRB will evaluate investigational device to determine or to concur with the PI whether it poses significant risk to subjects. A significant risk device means an investigational device that:

1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject.

2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject.

3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject.

4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

23. Institutional Review Board Operations.

a. Composition and Organization.

The constitution of the IRB will conform to the requirements of this Instruction and *(References b, d and t).*

1) The IRB will have a minimum of nine members and may have specified alternates.

2) The IRB will be composed of persons qualified through the maturity, experiences, expertise, education and diversity in racial and cultural background. IRB members must have knowledge and sensitivity to such issues as community attitudes and practices so as to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

3) In addition to possessing professional competence, the IRB will include persons knowledgeable and able to evaluate protocols in terms of organizational commitments and regulations, applicable law, and standards of professional conduct and practice.

4) The IRB will include at least one member who is not affiliated with USU, or part of the immediate family of a person affiliated with USU.

5) The IRB must have at least one member whose primary concern is non-scientific.

6) The IRB may have individuals who serve in more than one capacity, thus a lawyer may serve as a non-scientific member as well as an unaffiliated member.

7) An IRB member will not participate in the initial or continuing review of any project in which the member has a clear or potential conflicting interest, except to provide information requested by the IRB.

8) The HRPPO staff or IRB may invite individuals with competence or expertise in special areas in which a need has been identified, to assist the IRB's review of a protocol. These individuals may not vote with the IRB.

b. Appointments.

1) Method of Appointment.

The President of USU or IO designee will appoint IRB members in accordance with DoDI 3216.02 *(Reference e).*

c. Alternates.

1) The President of USU or IO designee may appoint an appropriate alternate for a member of the IRB. Alternate members will serve in the absence of a primary IRB member.

2) The alternate will have qualifications similar to the primary IRB member for whom he or she will serve.

3) An alternate member will vote on the IRB motions in place of the IRB member of whom he/she is representing as an alternate.

d. Ex-Officio Members.

The following will serve as permanent, non-voting, ex-officio members of the IRB:

1) The Vice President, Research or designee.

2) A representative from the Office of General Counsel.

3) Other individuals as designated by the USU Institutional Official.

e. Attendance.

1) IRB members shall give reasonable notice to the IRB Coordinator of an anticipated absence.

2) If an absence cannot reasonably be anticipated, such as illness or family emergency, the IRB member shall give notice at his/her earliest convenience.

3) The failure to attend three or more meetings without reasonable notice may be considered cause for removal.

f. IRB membership Appointment

The President, USU, or designee will appoint a member of the IRB as Chair. A Vice-Chair will also be appointed to serve in the Chair's absence. If neither Chair nor Vice-Chair is available, a senior IRB member or the Executive Secretary may Chair the meeting.

g. Term of Appointment.

1) The Chair shall be appointed for a three year term and may be extended at the discretion of the USU President or IO designee.

2) IRB members shall be appointed for a term of up to three years and may be reappointed.

h. Removal.

The USU President or IO designee may remove and/or replace the Chair, Vice Chair or an IRB member for, but not limited to the following reasons:

1) Misconduct.

2) Negligence or dereliction of his or her duties.

3) Chronic absenteeism as defined in section 23.e above.

4) Disclosure of confidential material or information.

i. Training or Continuing Education.

HRP training for IRB members will be provided in the form of written materials (e.g., texts, pamphlets, professional materials, journal and newspaper articles, etc.), website tutorials, personal instruction, in-house seminars, as well as local and national meetings, seminars and conferences, as institutional funding allows.

j. Voting.

1) Quorum.

a) At each meeting, the IRB will consist of

(1) A majority of the members including the Chair or Vice Chair, or his/her representative.

(2) One member whose background and primary concern is non-scientific.

(3) Members sufficiently diverse to have sufficient knowledge to review protocols from diverse research fields.

(4) Appropriate representation to properly review protocols, as determined by the Chairs and/or HRPP Director and IRB Coordinator.

(5) When reviewing studies of FDA-regulated test articles the presence of a physician will be required at a convened meeting.

2) IRB members must be present to vote.

Telephone or other electronic voting is permitted only when members actively participate in the discussion via speakerphone or video teleconferencing in real time.

3) Members shall review all the protocols on the agenda, participate in the deliberations and vote on the motions, as appropriate. When approving research that recruits subjects from a locality or organization, the IRB may request input from individuals within the locality or organization in support of the IRB's understanding of local context and to confirm the necessary subjects identified in the protocol are available *(References b, c, & a6).*

k. Consultants to the IRB.

The IRB may consult with any concerned person or group or subject matter expert within or outside USU. These individuals may not vote with the IRB.

l) Reports of Noncompliance.

The HRPP Director, on behalf of the IRB will report to the IO or designee any serious or continuing non-compliance with the requirements and determinations of the IRB by investigators. Circumstances and actions taken to correct serious or continuing non-compliance will also be reported to the CDO, in its USU oversight role.

m. Conflict of Interest.

1) IRB members with financial relationships or other personal considerations have the potential for conflicting interests in research. This potential conflict of interests must be resolved or eliminated as it may affect the rights and welfare of research subjects. 32 CFR 219.107 *(Reference b)* and 21 CFR 56.107 *(Reference d)* The IRB and investigators will be guided by the principles contained in DoD 5500.7-R *(Reference a5)*

2) Procedures.

a) IRB members will be reminded of conflict of interest policies prior to each meeting and will ensure that they are aware and maintain awareness of Federal regulations and institutional policies regarding financial relationships and interests in human subjects research.

b) The IRB Executive Secretary or designated IRB Coordinator will document any actions taken regarding potential conflicts of interest related to particular protocols.

c) IRB Review will help ensure that financial interests do not compromise the rights and welfare of human research subjects by determining:

(1) Mechanisms to eliminate the potential conflict of interests of parties involved in the research.

(2) Other actions necessary to minimize risks to subjects.

(3) The information to be disclosed to research subjects regarding the source of funding, funding arrangements, financial interests of parties involved in the research, and any financial interest management techniques applied.

3) Investigators:

a) Will consider the potential effects that a financial relationship of any kind might have on the research or on interactions with research subjects, and what actions to take.

b) Include information in the informed consent document such as the source of funding and funding arrangements for the conduct and review of research, or information about a financial arrangement of an institution or an investigator and how it is being managed.

c) Use special measures for PI's to implement when a potential or actual conflict exists, such as:

(1) Having a member of the research team, other than the investigator with a potential conflict, obtain consent during the informed consent process.

(2) Using independent monitoring of the research.

n. Roles and Responsibilities.

1) Duties of the IRB Chairs.

a) Preside over convened meetings.

b) Request that the PI be present to answer questions during the meeting, if this is determined to be necessary.

c) Perform expedited review of studies involving no more than minimal risk, per the categories for expedited review contained in the Expedited Review Procedure appendix in *(Reference u),* or for protocol changes that are considered to reduce or have no effect on risk to the subjects in approved research. The Chairs may:

(1) Delegate, at his or her discretion, part or all of such expedited review to experienced IRB members.

(2) Exercise all of the IRB's authority during expedited review except that of disapproval of a study, which may only be determined by the convened IRB.

d) Hold in abeyance an ongoing study until the convened committee can review in cases where harm to human subjects, noncompliance with Federal regulations and/or this policy, or misconduct is suspected.

2) Duties of the IRB Coordinator.

As delegated by the HRPP Director/Executive Secretary, the IRB Coordinator is responsible for:

a) Performing initial review of all protocols involving human subjects research and determine the level of IRB review with the concurrence of the IRB Chairs.

b) Preparing the agenda and distributing supporting written material.

c) Forwarding a copy of each protocol to receive full review to each member of the IRB at least seven days prior to the meeting, or where appropriate, forward protocols to the Chairs or designated member for expedited or concurrence rev1ews.

d) Requesting that the PI be present to answer questions during the meeting if this is determined necessary.

e) Preparing minutes of the meeting showing:

(1) Actions taken by the IRB.

(2) The number voting for/against and abstaining on each action.

(3) The basis for requiring changes in or disapproving research.

(4) A written summary of the discussion of controversial issues and their resolution.

f) Recording IRB member attendance.

g) Providing a written report on all research protocols given expedited or exempt review to the IRB.

h) Reporting to the IRB any inquiries or expedited protocol changes concerning research that is being conducted.

i) Notifying PI's in writing of IRB determinations and recommendations that apply to them, including all specific actions that must be completed prior to approval (project assurances requirements, written approvals from all IRBs involved, approved informed consent form, written approval of all modifications).

j) Notifying PI's prior to the time that annual human research review is required.

k) Furnishing Federal regulations, copies of References, journal articles, and other relevant material to the IRB.

l) Meeting periodically with the IRB Chairs or the IRB itself to discuss possible changes in IRB procedures and prepare such revisions for approval by the IO or designee.

m) Making available to the IO or designee, protocols which have been approved by the IRB.

n) Ensuring that USU personnel complete human subjects training in accordance with applicable instructions and maintain a record of such training.

o) Maintaining records for 10 years after completion of the research of:

(1) Continuing review activities.

(2) Correspondence between the IRB and the investigators.

(3) A list of IRB members.

(4) Statements of significant new findings provided to subjects.

p) Reviewing proposed exceptions to policy to ensure compliance with applicable regulations and forward to the IRB with an assessment of the proposed exception.

3) Duties of the Exemption Determination Official/s (EDO). EDO(s) will have the following authorities and responsibilities:

a) Determine the applicability of 32 CFR 219 to USU research activities.

b) Determine which USU human subjects activities are exempt from IRB requirements under 32 CFR 219.

c) Perform an administrative review for contractor conducted research that the primary IRB has determined to be exempt.

d) Maintain records of EDO activities in sufficient detail that an outside reviewer can verify the correct application of statutory, regulatory, and policy requirements.

4) Duties of the HRPO: The HRPP Director, and /or other duly appointed HRP staff serving as the HRPO, have the authorities and responsibilities which include, but are not limited to, the following:

a) Responsible for the shared management of the human research protection program including the authority to:

(1) Develop procedures to implement policies that apply to USU's extramural HRPP activities.

(2) Conduct program reviews and quality improvement activities.

(3) Review reports of allegations of non-compliance or research misconduct from extramural sites, assuring resolution at the appropriate level and reporting as required.

b) Responsible for conducting timely and effective reviews of research to include:

(1) Authority to accept the official notification to DoD by the institution receiving DoD support certifying that research involving human subjects has been approved by the IRB in accordance with USU's Assurance.

(2) Authority to conduct administrative reviews of non-exempt research involving human subjects conducted by USU billeted or student investigator where there is an existing Institutional Agreement for IRB Review with another DoD institution.

(3) Authority to determine whether research protocols involving human subjects comply with all DoD requirements.

c) Responsible for maintaining records of all determinations.

5) Duties of IRB Members:

a) Be knowledgeable of the relevant regulations, instructions, and directives dealing with human subject research.

b) Examine the protocols with respect to human subjects' protections issues.

c) Assess the risk-benefit ratio while ensuring that the risks are minimized and the potential benefits are maximized.

d) Obtain clarification from the PI or consult appropriate literature or experts if a protocol is unclear or raises questions.

e) Ensure that the study is ethically and scientifically sound.

f) Vote for approval, disapproval, deferral (tabling), or modification of protocols, or

require full reviews of protocols that have been reviewed via expedited review procedures.

g) Participate in subcommittees to address policies and procedures on particular issues or for special purposes as requested by the Chairs.

6) Duties of the HRPP Director:

a) Serve as the designated HRPO and HPA for the USU Federal Wide Assurance and liaison between the IRB Office, regulatory agencies, USU Departments, investigators, and research programs.

b) Work directly with investigators, as needed, to ensure that human research protocols comply with all applicable standards throughout the life of the protocol.

c) Supervise the IRB administrative support staff and review correspondence that conveys IRB deliberations and contingencies for approval of research activities involving human subjects.

d) Serve as the human subject protections expert advisor to the IRB and provide updates to the IO as requested, but not less than annually.

o. Schedule of Meetings.

Scheduled meetings are held monthly. Unscheduled meetings may also be arranged as necessary and IRB members will be given adequate time to review the meeting materials.

p. IRB Review Procedures.

1) Protocols are reviewed by the IRB only after they have been reviewed and recommended by the Office of the Vice President, Research. Grant applications, along with the IRB Protocol Application Form will be reviewed by the IRB and should be accompanied by documentation that provides sufficient supplementary information necessary for review.

2) Intramural protocols will generally be reviewed by the IRB after approval by the USU Scientific Merit Review Committee for both intramurally funded and any non-funded human research protocols conducted by USU investigators. Scientific Review from the National Institutes of Health (NIH) and from other extramurally funded research sponsor is generally accepted and may not require further USU Scientific Review.

3) Extramural projects will generally be reviewed by the IRB upon notification of funding by the Director, OSP (just-in-time review).

4) All decisions of the IRB will be made with a quorum present and with at least one member whose primary concern is non-scientific, consistent with *(Reference b, c and d)* Decisions will be based upon the majority vote of those members at the meeting.

5) All members (or their alternates) will receive complete study documentation for review.

6) Each member must review the protocol to participate in IRB deliberation except for reviews where the expedited or concurrence review procedure applies. Members may request additional information on any protocol reviewed by such procedures and request that such a protocol be reviewed by the convened board at its next scheduled meeting.

7) The Chair or Executive Secretary of the IRB may request that the PI and advisor, if a student investigator, attend part of the IRB meeting to provide information and answer questions.

a) The PI will be excused before the IRB resumes deliberations concerning the protocol.

b) Even if not requested to attend, the IRB Coordinator shall ensure that the PI or his/her representative will be available when his/her protocol is on the IRB agenda in case the IRB raises questions.

8) The IRB will make one of several determinations, based upon the majority vote of members present. The Chair has the option to abstain and vote only to break a tie or to meet the quorum requirement at a convened meeting. Although the aim is to achieve consensus, it is understood that this may not occur. The IRB minutes will document the dissenting or abstaining members' reasons for their non-concurrence with the majority vote.

a) Approve:

(1) Approved, as submitted.

(2) Pending approval, contingent upon specific modifications being made.

b) Deferral:

(1) The protocol cannot be approved without additional information (the IRB will specify the information needed and who will be responsible for gathering it). Providing the additional information does not guarantee approval.

(2) Cannot be approved at this time because major modifications are needed.

c) Disapprove:

(1) Under the authority or signature of the appropriate Federal HRP official, the IRB, through the IRB Coordinator will provide written notice to the PI.

(2) If the IRB disapproves or defers the research study, the notice will include reasons for the decision.

(3) The PI may respond in writing or appeal the IRB's notice of deferral or disapproval by requesting to present, in person, his/her case for appeal at the convened IRB meeting.

9) Scope of IRB Review.

a) The IRB will review and approve, require modifications in, or disapprove human research activities covered by this Instruction.

b) The IRB will require that information given to subjects as part of informed consent is in accordance with *(References b through e).* The IRB may require that the subject receive additional information if the IRB determines it would add meaningfully to the information provided to the subject.

c) The IRB will require documentation of informed consent or may modify or waive documentation in accordance with *(References b, c and g).*

d) The IRB will provide PIs with a written notice of its decisions.

q. Suspension or Termination.

1) The IRB has the authority to hold in abeyance, suspend, or terminate approval of research that is not being conducted in accordance with the requirements or that has been associated with unexpected harm to subjects or unanticipated problems.

2) The Chairs may act immediately on behalf of the IRB to hold in abeyance, suspend, or terminate approval of research. These actions will be reviewed at the next meeting of the IRB and affirmed or modified by the convened IRB.

3) If the IRB suspends or terminates approval for regulatory noncompliance, it will notify and provide the rationale for the action to the PI, the IO or designee, the CDO and other Federal officials/ oversight agencies as required.

4) Abeyance is a local IRB action that involves a temporary halt to some or all protocol activities in order to correct a deficiency. A protocol may be placed in abeyance by the Chairs or convened IRB in cases of regulatory or protocol non-compliance that must be corrected but does not present an increased risk to human subjects. The PI and appropriate institutional authorities will be notified in the event a protocol is placed in abeyance.

r. Procedure to submit a protocol for IRB review.

1) Investigators will submit complete protocols and consent forms in accordance with this

Instruction. The documents become part of the permanent records of the IRB and may be inspected and reviewed by various government agencies. The IRB does not act on incomplete protocols and these will be returned to the investigator for completion.

2) The completed protocol package should contain the protocol, informed consent document and HIPAA authorization forms (if required), copies of case report forms and/or data collection instruments, scripts to be used for telephone interviews, Clinical Investigator's Brochure (if applicable), human subjects protections training certification for members of the research team that interact with subjects or use protected health information (PHI), Researcher's Responsibility Forms, Conflict of Interest disclosure forms, DMRN Cover Sheet, copies of IRB approval documentation for studies reviewed at other institutions, and copies of recruitment materials (e.g., advertisement, announcements, radio or TV scripts, texts of letters or emails to be sent to subjects, etc.).

3) The type of review required (i.e. full, expedited, or exempt) will be recommended or concurred by the IRB Coordinator or member of the HRP staff.

s. Review and Approval Timeline.

1) Pre-IRB Evaluation of New Protocols.

After receipt by the HRPPO, protocols are generally evaluated within five working days and the PI will be notified of any changes or additions necessary to complete the pre-IRB review. The PI will provide the revised documents to comply with the IRB Coordinator's request for additional information or revisions within five working days. After a protocol is determined to contain all components necessary for IRB review, it will be forwarded to the convened IRB for review or to the Chairs or EDO for administrative review, as appropriate.

2) Administrative Review Timeline.

As a planning guideline, investigators should anticipate a 30 working day period from the time protocols are received by the IRB office for protocols that are approved through the expedited or exempt process. However, the time required for review of a given protocol will vary depending on the nature of the protocol, any components that must be added or modified prior to IRB review, and current HRPP Office workload conditions.

3) Full Board Review Timeline.

Protocols that require full IRB review will be scheduled in accordance with the schedule and guidance issued by the HRPP Office. As a planning guideline, investigators should anticipate a 15 working day period following the date of a review by the convened IRB for formal announcement of results.

4) "Just in Time" Review.

Protocols that require funding for execution but have not been approved for funding will not be reviewed by the IRB. However, if extenuating circumstances exist, a "just-in-time" assurance memo will be provided that states IRB review will be conducted, as appropriate.

t. Period of Approval and Continuation.

1) IRB approval for human research is granted for a specific period of time. For protocols in which the USU IRB is considered to be the IRB of Record, the IRB's approval expiration date will be shown on the IRB approval memo provided to the PI.

2) Protocols approved through review by the convened IRB, and through the expedited process, will be for a period not to exceed one year.

3) Protocols approved through the exempt process will not require further IRB review. All modifications or changes to exempt protocols must be submitted to the EDO or IRB for approval, prior to implementation.

4) The IRB may decide that more frequent review is necessary for greater than minimal risk protocols and may grant approval for a shorter period.

5) Although PI's will be sent continuing review reminder notices before the protocol approval expiration date, it is the PI's ultimate responsibility to ensure that the study's IRB approval does not expire. To ensure that the HRPPO has sufficient time to process continuing review paperwork, the PI should plan to submit continuation paperwork 20-45 days prior to the date of the study's approval expiration date for studies determined to be minimal risk and 60-90 days for studies determined to be "greater than minimal risk." Studies that were approved initially by the convened IRB may require additional processing time. For planning purposes, the PI's should take into account that, regardless of the type of initial review, continuing review procedures may require an onsite inspection/audit (e.g., observation of consent process, consent form and records review, etc.) prior to the study being considered by the IRB for continued approval.

6) IRB approval will automatically terminate at the end of the approval period. A study may be placed in abeyance for up to 60 days following expiration of IRB approval in order to allow the PI additional time to prepare a request for continuation. No study activity may occur during the period of abeyance. If no request for continuation is received within 60 days after the expiration of IRB approval the protocol will be permanently closed for human subjects participation. This closure will be reported to the Office of the Vice President for Research in order to reconcile the closure with the terms of the grant, as applicable.

7) Depending upon the type of study and in concert with Federal guidelines and regulations (e.g., FDA requirements) some studies may continue to remain open and under IRB oversight during the period of data analysis, after subject interactions and data collection are complete.

u. Changes in the Protocol after Initial Approval.

1) IRB approval is only for the described study that was reviewed by the IRB. Any

modification(s) to the approved protocol must be prospectively approved by the IRB before implementation. A revised protocol with the changes noted must be submitted with the request for change.

2) If any part of the research is to be conducted at another institution, its appropriate approving authority also must approve changes in the protocol. Any and all changes in the protocol or consent form required by the off-site facility must be submitted to the USU IRB for review prior to implementation, including the accrual of research subjects.

3) Unexpected situations may require the PI to modify the consent form or modify or suspend the study. If an unanticipated problem that, in the PI's best judgment, may be related or possibly related to the research, resulting in injury or places subjects or others at a greater risk of harm, the PI must immediately (within 24 hours) notify the IRB Chair, HRPP Director and Research Monitor if one is assigned. Initial notification may be via direct communication email (preferred) or fax, with a formal written report that contains all available relevant information.

v. IRB Review Fees.

For research supported by commercial sources, reimbursement will be included as a direct cost.

w. Waiver of Provisions of the Instruction.

Certain circumstances may require exceptions to provisions of this Instruction. Waivers can only be considered within the guidelines of Federal regulations and must be reviewed by the HRPP Director. PI's should prepare a memorandum justifying any proposed exception to policy and submit to the IO via the HRPP Director.

24. HRP Compliance/Quality Assurance Monitoring.

As directed by the IRB or HRPP Director, member(s) of the HRPP staff or IRB will conduct on-site inspections or audits of human research activities related to protocols that have been reviewed and approved by the USU IRB. Findings will be reported at the convened IRB meeting.

CRITERIA FOR EXEMPT AND EXPEDITED REVIEW

1. General.

a. The Exemption Determination Official(s) (EDOs) will evaluate research protocols to determine if criteria for exemption or expedited approval under DoD/DHHS ("Common Rule") regulations are met *(References b, c and u)*. Only "no more than minimal risk" studies may be administratively approved by the EDO or the IRB Chair/designee, as applicable.

b. In accordance with 32 CFR 219.110 *(Reference b),* all administratively reviewed intramural human research protocols will be made available, via the University's electronic protocol submission system, to members of the fully convened IRB, who may, in turn, administratively accept approval, recommend modification, request a full review, or recommend other actions. Approval of administratively reviewed protocols is final when the IO or designee approves the final minutes and Review of Administrative Actions Report.

2. Criteria for exempt research *(Reference b and c)*.

a. Research conducted in established or commonly accepted educational settings involving normal educational practices, such as:

1) Research on regular and special education instructional strategies.

2) Research on the effectiveness of, or the comparison among, instructional techniques, curricula, or classroom management methods.

b. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement) if information taken from these sources is recorded in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

c. Research involving survey or interview procedures, except where the following conditions exist:

1) Responses are recorded in such a manner that the human subjects can be identified, directly or through identifiers linked to the subjects.

2) The subject's responses, if they became known outside the research, could reasonably place the subject at risk of the subject's financial standing or employability.

3) The research deals with sensitive aspects of the subject's own behavior, such as illegal conduct, drug use, sexual behavior, or use of alcohol. Research involving survey or interview procedures can be exempt when the respondents are elected or appointed public officials or candidates for public office.

d. Research involving the observation (including observation by participants) of public behavior, except where any of the following conditions exist:

1) Observations are recorded in such a manner that the human subjects can be identified directly or through identifiers linked to the subjects.

2) The observations recorded about the individual, if they became known outside the research, could reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing or employability.

3) The research deals with sensitive aspects of the subject's own behavior such as illegal conduct, drug use, sexual behavior, or use of alcohol.

e. Research involving the collection or study of existing data, documents, records, pathological 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.

3. Criteria for review via the expedited process.

a. Clinical studies of drugs and medical devices only when conditions (a) or (b) are met:

1) Research on drugs or devices for which an investigational device exemption is not required.

2) Research on medical devices for which (i) an investigational device exemption application 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.

b. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

1) From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amount drawn may not exceed 550 ml in an eight week period, and no more than two times per week.

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

c. Prospective collection of biological specimens for research purposes by non-invasive means:

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

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

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

4) Excreta and external secretions (including sweat).

5) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a diluted citric solution to the tongue.

6) Placenta removed at delivery.

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

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

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

10) Sputum collected after saline mist nebulization.

d. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. When medical devices are employed, they must be cleared/approved for marketing. Examples include:

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

2) Weighing or testing sensory acuity.

(3) Magnetic resonance imaging.

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

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

e. 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).

f. Collection of data from voice, video, or image recordings made for research purposes.

g. Research of individual or group characteristics or behavior (including, but not limited to, research involving perception, cognition, motivation, identity, language communication, cultural beliefs or practices, and social behavior) employing surveys, interviews, oral histories, focus groups, program evaluations, human factors evaluations, or quality assurance methodologies.

h. Continuing reviews of research previously approved by the convened IRB as follows:

1) 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.

2) Where the research remains active only for the purposes of data analysis.

3) Where no subjects have been enrolled and no additional risks have been identified.

i. Continuing reviews of research not conducted under an investigational device exemption where categories two through eight do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risks and no additional risks have been identified.

THE USE OF HUMAN TISSUE/SPECIMENS AND/OR DATA IN RESEARCH

1. General

Biological specimens (e.g. tissue, blood, urine) and data from human subjects may be collected either retrospectively or prospectively. In this section, guidelines for use of "specimens," refers both to biological samples and data from humans.

2. Retrospective collection refers to existing specimens (i.e. tissue, blood, urine, etc.) which have been collected, are "on the shelf," and have previously been stored at the time that the protocol is submitted for review to the IRB, and:

a. The specimens were collected for research but for a different project to that which is being proposed; or,

b. The specimens were obtained for clinical assessment for routine examination, for diagnosis, or during the course of treatment.

3. Prospective collection consists of specimens which have not yet been collected at the time the protocol is submitted for review to the IRB.

a. The procedures to be performed are specifically for research purposes (e.g., additional blood at time of clinical venipuncture, additional biopsy material collected, normal control blood drawing).

b. The specimens are to be obtained from future discarded samples obtained in the routine course examination, diagnosis and/or treatment (e.g., tumor tissue from newly diagnosed patients, left over urine/blood after clinical tests, etc.).

4. Samples or data in which personal identifiers have been removed or meet defined criteria may be classified as non-human subjects research and thus not require IRB review. These criteria are defined below.

5. Use of specimens or data linked to identifiers may be considered human subjects research depending on access to the link. Subject's consent is required for the use of specimens/data prospectively collected. Reconsent is required for use of the specimens/data that differs from the purposes of the original protocol.

6. Protocols utilizing specimens/data that were collected retrospectively or specimens/data to be collected in the future (such as medical records; and ongoing collection of specimens for a tissue repository) and they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through any coding systems, may be considered as non-human subjects

research provided that:

a. The specimens/data were not collected specifically for the current proposed research project through an interaction or intervention with living individuals.

b. The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded specimens/data pertain because, for example:

1) The key to decipher the code is destroyed before the research begins.

2) 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.

3) 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.

4) There are other legal requirements prohibiting the releases of the key to the investigators, until the individuals are deceased.

7. In protocols utilizing specimens and/or data that are identifiable either directly or through the use of codes, written consent/reconsent may be waived by the IRB if the study meets all of the following requirements:

a. The research presents no more than minimal risk.

b. Conducting the research without a waiver is impracticable.

c. The waiver will not adversely affect the subjects' rights or welfare.

d. The subject has waived reconsent in the original consent document or authorized other uses of their specimens.

e. Pertinent information will be provided to subjects if deemed appropriate by the IRB.

8. In studies that use specimens/data that are collected prospectively and obtained expressly and specifically for research purposes, the protocol will be reviewed by the IRB. Consent is required for specimens/data collected prospectively for research whether they are:

a. Identifiable directly or through the use of coded identifiers known to the investigator.

b. Linked by identifiers unknown to the investigator.

c. Linked by identifiers known only to a third party or intermediate entity and unknown by the investigator.

9. The following pertains to specimens that are collected prospectively for clinical assessment during routine examination, for diagnosis, or during the course of treatment, and that become future discarded clinical samples:

a. Protocols utilizing specimens that are tied to identifiers known only to a third party or intermediate entity will be given IRB review but the requirements for consent may be modified by the IRB. If the principal investigator later needs additional information from the chart, the IRB will again review the proposed process to be used to ensure patient privacy.

10. Generally, re-contact of a subject is prohibited whether the purpose for the re-contact is for re-consent for future research or because of research results unless:

a. The subject has consented to re-contact and/or re-consent.

b. An unexpected epidemiological finding of importance is identified after the specimen was collected.

c. The original diagnosis is found to be incorrect and the results suggest that a different course of treatment is appropriate.

11. For secondary use of specimens, if subsequent investigators may be given access to the samples with direct or indirect identifiers, the consent document should state this and should give the subject the option of consenting to future use in other future research. The consent process should inform subjects that they may be re-contacted or give subjects the option of not being re-contacted. The consent should also give the subject the option of limiting or specifying the future use of the sample.

12. In addition to the policy, rules and guidelines concerning informed consent contained elsewhere in the body of this Instruction or in the Appendix, consent documents for genetic research will inform subjects of:

a. The possible commercial value arising out of the research, and if applicable, whether the subject will retain any proprietary interest in the sample and/or whether the subject will receive any share in profits from commercial development.

b. The information the subject is entitled to receive, if any. If there is to be no or limited disclosure, the consent should explain the reasons. If some or all findings are to be disclosed, the consent should set forth disclosure procedures.

13. As to matters concerning genetic research, if any of the provisions contained in this section are in conflict with other provisions contained in this Instruction, the provisions of this section will be deemed controlling.

14. When tissue/samples are received from or sent to a source outside DoD, in addition to the above, a Material Transfer Agreement (MTA) is required. MTAs are handled through the Joint Office of Technology/Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.

DETERMINATION OF NON-HUMAN SUBJECTS RESEARCH STATUS

1. Overview.

IRB review is required if you are engaged in human subjects research. Certain activities that incorporate scientific research methodologies may not be classified as human subjects research and therefore do not require review by the IRB. This determination is made by the Exemption Determination Official (EDO). Investigators will be informed of a non-human subjects research determination in writing by the EDO.

Depending on the plan for dissemination of results, IRB review may be required or prudent. Today, many scholarly journals require certification of IRB approval before accepting a manuscript for publication that involves human data. Investigators should keep in mind that retrospective IRB approval is not permissible; therefore, if there is an intent to disseminate results in the open scientific literature or use data beyond the activities defined below, prospective IRB review is strongly recommended.

2. Examples of activities that may be classified as non-human subjects research:

a. Health surveillance.

This refers to activities such as those carried out under 10 USC 1074f (medical tracking for members deployed overseas). Health surveillance is part of the medical care and public health care functions of the Military Health System.

b. Medical quality assurance.

Although medical quality assurance activities may employ scientific methods of review, it is not conducted for human research purposes *(Reference a9)*.

c. Program evaluation.

This refers to assessments of the success of established programs in achieving objectives when the assessments are for the use of DoD program managers, for example, a survey to determine if program beneficiaries are aware of the availability of program services or benefits. However, if it were an assessment carried out for publication in general literature regarding a non-DoD program of a similar type, it would be considered research and subject to IRB review.

d. Customer satisfaction surveys.

This refers to surveys of program users to obtain feedback for program managers. This is similar to program evaluation.

e. Operational test and evaluation.

This refers to activities defined as "field test, under realistic combat conditions, of any item of (or key component of) weapons, equipment, or munitions for the purpose of determining the effectiveness and suitability of the weapons, equipment, or munitions for use in combat by

typical military users; and the evaluation of the results of such test " *(Reference a10).* If the purpose of the test is to obtain data on the effects of non-routine interaction with an individual, it would be considered human subjects research.

f. Simulation training and assessments.

Simulation training or technology assessments that are integrated into the medical curriculum and involve student use of mannequins or non-human simulation tools shall not be considered human subjects research unless there is an intent to generate or use information collected as data in a research context, abstract, presentation, or publication.

g. Analysis of aggregate-level datasets.

Aggregate-level datasets may be based on individual-level human data but will not contain any individual level information. Examples of aggregate-level data include a dataset containing disease morbidity rates for a set of geographic locations or population categories, or organizational level information such as average scores for a measure (e.g., average PT scores for a set of units). If an investigator has access to individual level data the research is generally considered human subjects research and is subject to IRB review.

h. Individual-level data under specific circumstances.

Personally Identifiable Information (PII) means information about an individual that identifies, links, relates, or is unique to, or describes him or her, e.g., a social security number; age; military rank; civilian grade; marital status; race; salary; home/office phone numbers; other demographic, biometric, personnel, medical, and financial information, etc. Such information is also known as PII (i.e., information which can be used to distinguish or trace an individual's identity, such as their name, social security number, date and place of birth, mother's maiden name, and biometric records, including any other personal information which is linked or linkable to a specified individual). *(Reference a8)*

Pre-existing data or specimens that meet the following criteria may be classified by the EDO as non-human subjects research:

1) Data or specimens that were not collected specifically for the current 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) from whom the data or specimens originated because of any of the following:

a) Any key linking the data or samples to identifying information is destroyed before the research begins;

b) The investigator(s) and the holder of a key enter into a formal agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased.

c) There are other legal requirements prohibiting the release of the key to the investigator(s), until the individuals are deceased.

d) Tissue samples without identifiers obtained from commercial sources. Research that uses immortalized cell lines obtained from commercial sources (for example, ATCC) will not be considered human subjects research. In such protocols submitted to the Office of the Vice President, Research, investigators will indicate the commercial source and specific cell lines that will be used.

EMERGENCY RESEARCH CONSENT WAIVER UNDER FDA REGULATIONS AT 21 CFR 50.24

The Secretary of Defense may waive the prohibition for informed consent under 10 USC 980 with respect to a specific research project to advance the development of a medical product necessary to the armed forces if the research project may directly benefit the subject and is carried out in accordance with all other applicable laws, including 21 CFR 50.24.

1. General.

Under FDA regulations defined at 21 CFR 50.24 it is possible to waive the general requirements or informed consent, termed an "Emergency Research Consent Waiver," for a class of research consisting of activities that have met the following strictly limited conditions detailed below.

2. Criteria.

The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

a. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

b. Obtaining informed consent is not feasible because:

1) The subjects will not be able to give their informed consent as a result of their medical condition.

2) The intervention involved in the research must be administered before consent from the subjects legally authorized representatives is feasible.

3) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.

c. Participation in the research holds out the prospect of direct benefit to the subjects because:

1) Subjects are facing a life-threatening situation that necessitates intervention.

2) Appropriate animal and other preclinical studies have been conducted and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects.

3) Risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

d. The research could not practicably be carried out without the waiver.

e. The proposed research protocol defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent.

The investigator will summarize efforts made to contact representatives and make this information available to the IRB at the time of continuing review.

f. The IRB has reviewed and approved informed consent procedures and an informed consent document in accordance with 21 CFR 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the research consistent with paragraph (b)(7) of this section.

g. Additional protections of the rights and welfare of the subjects will be provided, including, at least:

1) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research will be conducted and from which the subjects will be drawn.

2) Public disclosure to the communities in which the research will be conducted and from which the subjects will be drawn, prior to initiation of the research, of plans for the research and its risks and expected benefits.

3) Public disclosure of sufficient information following completion of the research to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results.

4) Establishment of an independent data monitoring committee to exercise oversight of the research.

5) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the research. The investigator will summarize efforts made to contact family members and make this

information available to the IRB at the time of continuing review.

3. Additional Requirements.

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

b. The IRB determinations required by paragraph (b) of this section and the documentation required by paragraph (c.4.) of this section are to be retained by the IRB for at least ten years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 21 CFR 56.115(b).

c. Protocols involving an exception to the informed consent requirement under this section must be performed under a separate FDA application that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols separate from an IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under Sec. 312.30 or 812.35 of 21 CFR.

d. If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (b) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to the FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

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

ADVERSE EVENTS REPORTING POLICY AND GUIDELINES FOR MILITARY RESEARCH

A. References

Institutions engaged in human subjects research conducted or supported by DoD and DHHS must have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of any unanticipated problems involving risks to subjects or others. (32 CFR part 219.103,45 CFR part 46.103, and 21 CFR part 56.108) and

U.S. DHHS FDA CDER CBER Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies- Small Entity Compliance Guide December 2012, Drug Safety

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

B. Applicability

1. This policy applies to all research conducted at the USU and other institutions in the National Capital Region that subscribe to this policy for reporting unanticipated problems involving risks to subjects or others and adverse events. It is the responsibility of the PI to report adverse events to the IRB. Unanticipated problems must be promptly reported, in accordance with this policy and guidelines, to the appropriate Department of Clinical Investigation (DCI) where the research is being conducted or the HRPP Director, for IRB review, consideration of substantive changes to the research protocol or informed consent process/document(s) or other corrective actions in order to protect the safety, welfare, or rights of subjects. The IRB will assess the degree of risk of harm and significance of the adverse event and has the authority to suspend or terminate research that is deemed harmful if continued (45 CFR 46.113).

2. Unanticipated problems are not limited to physical harms. They can include breaches of confidentiality or emotional harms (such as the emotional distress that could be triggered by questions about traumatic life events). Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. See *(Reference al)* for examples of unanticipated problems that do not involve adverse events but must be reported under the HHS regulations at 45 CFR 46.103(a) and 46.103(b) (5).

3. The IRB relies on the integrity and expertise of investigators, and their Research Monitors (if applicable), to assess whether an adverse event is an unanticipated problem. Investigators are to provide their judgment on the Adverse Event Report Form, which can be accessed via the USU IRB electronic protocol submission website, whether the problem requires modifications

of the informed consent document or process and/or change in the protocol in order to minimize risks to subjects, and whether information about the adverse event is germane to consent and/or re-consent/notification of subjects already enrolled. Investigators, and their Research Monitors, as applicable, are to provide their assessments of the significance of the adverse event including protocol deviations/violations that result in increased risk to subjects or others, affect the rights, safety or welfare of subjects, affect the integrity of the study. This must be reported to the IRB including the measures undertaken by the PI to eliminate apparent immediate hazards to the subject(s) or to protect the life or physical wellbeing of the subject.

C. Definitions:

1. *Unanticipated Problem (UP) involving risks to subjects or others* –An Unanticipated Problem involving risk to the subject or others is defined as any incident, experience, or outcome that meets all of the following criteria:

a) *Unexpected* (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied.

b) *Related or Possibly Related* to participation in the research *(possibly* related means there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research).

c) Suggests that the research places subjects or others at *a greater risk of harm* (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

A UP may only involve exposure of a subject or others to an unexpected risk or the risk may culminate in a subject or another individual actually experiencing a harm that is generally described as an adverse event in clinical research or an adverse outcome in behavioral or social science research.

2. *Adverse Event (AE)* - Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. The AE may be expected or unexpected, and related or unrelated to the subject's participation in the research. The majority of adverse events occurring in human subjects are not UPs. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research; on occasion, they can occur in the context of social and behavioral research.

3. *Unexpected AE* is one in which the nature, severity, or frequency of the AE is *not* consistent with any of the following: (a) Investigator's brochure, (b) Investigation plan or

application, (c) IRB approved research protocol, (d) IRB approved informed consent document, (e) other relevant sources of information, such as labeling and package inserts, (f) HIPAA Authorization document or any confidentiality protection document, or (g) the reasonably expected natural history and progression of the underlying disease or condition of the subject(s) experiencing the adverse event.

4. *Related AE* is one for which there is reasonable information (e.g., strong temporal relationship, clinical indication) that the AE may have been at least partially caused by the procedures involved in the research (e.g., the use of the drug, device, or intervention).

5. *Possibly Related AE* means there is a reasonable possibility that the adverse event, incident, experience, or outcome may have been caused by the procedures involved in the research (e.g., the use of the drug, device, or intervention); however, there is insufficient information to determine the likelihood of this possibility.

6. *Unrelated AE* is one where there is no information or reason to attribute the AE or problem to procedures involved in the research (e.g., the use of drug, device, or intervention).

7. *Serious AE (SAE)* is an adverse event that results in any of the following outcomes:

a) Fatal (death).

b) Life-threatening.

c) In-patient hospitalization or prolongation of existing hospitalization.

d) Persistent or significant disability/incapacity.

e) Congenital anomalies or birth defect.

f) Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

8. *Internal Adverse Event* is when the adverse event or incident is experienced by subjects enrolled by the investigator(s) at their institution (example: USU).

9. *External Adverse Event* is when the adverse event or incident is experienced by subjects enrolled by investigators at other institutions engaged in a multi-center study.

D. Reporting an *Unanticipated Problem*

1. Determine if an Adverse Event is an Unanticipated Problem:
a) Is the adverse event unexpected? (Refer to section c.3).

b) Is the adverse event related or possibly related to participation in the research? (Refer to sections c.4 and c.5).

c) Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized? (Refer to section c.7). If the answer to all three questions is yes, then the adverse event is an unanticipated problem and must be promptly reported to the USU IRB.

2. Reporting Procedure and Guidelines
a) If a serious or unexpected adverse event requires an immediate change to a protocol in order to eliminate an apparent immediate hazard to research subjects, the investigator may implement the change necessary to protect the welfare of the research subjects.

Notify the USU IRB point of contact (POC) prior to implementation of the protocol change and submit an AE report with an addendum to the USU IRB within 48 hours, describing the change and events that necessitated immediate implementation:

POC: USU HRPP Director: (301) 295-3836

b) The prompt reporting procedure is accomplished by submitting a completed AE Report Form. For protocols involving investigational drugs or devices, the PI must also report to the sponsor of the IND or IDE immediately within the sponsor's required time frame (usually 24 hours).

c) The PI must provide a copy of the adverse event report to the Research Monitor of the protocol for review and signature.

d) The National Capital Region's Policy requires reporting of Adverse Events at the time of continuing review. The adverse event-reporting log should be submitted with USU continuing review paperwork.

3. Report of Internal Adverse Events Time Line and Format (Refer to Table 1 for the AE reporting categories. Use the Internal AE Report Form for all internal adverse events.)

a) Category 1: All unanticipated problems involving risks to subjects or others and adverse events. Thus, any internal AE that is unexpected and serious, and in the opinion of the PI, related or possibly related to the subjects' participation in the research, must be promptly

reported by the PI to the USU IRB (as appropriate) with the following time line:

1) Fatal - within 48 hours (2 working days)

2) Life threatening - within 2 weeks (10 working days)

3) All others- within 2 weeks (10 working days)

b) Category 2: Any internal AE that is expected and serious and, in the PI's opinion, is related or possibly related to the subjects' participation in the research, must be promptly reported by the PI to the IRB:

1) Fatal - within 48 hours (two working days)

2) Life threatening - within two weeks (10 working days)

3) All others-within two weeks (10 working days)

c) Category 3: Any internal AE that is unexpected and *non-serious,* and in the PI's opinion that is *related or possibly related* to the subjects' participation in the research must be reported by the PI to the IRB within two weeks (10 working days).

d) Category 4: Any other adverse events in the PI's opinion that may jeopardize the subject's health, confidentiality or well-being should be reported by the PI to the appropriate IRB within two weeks (10 working days).(e) Category 5: Unanticipated problems involving breach of confidentiality/privacy or HIPAA violation which places subjects or others at a greater risk of harm (including physical, psychological, economical, or social harm was not previously known or recognized must be reported promptly two weeks (10 working days) from the PI notification of the event, using the Internal AE Report Form.

f) All other internal AEs that are either not serious and have been described on the informed consent or serious but definitely unrelated to the research and did not meet the prompt report criteria may be reported on the annual progress report (APR) during the continuing review of the protocol.

4. Report of External Adverse Events Time Line and the format for multi-center studies, any external AE that occurs at other institutions must be reported to the appropriate IRB in accordance with the reporting guidelines and procedures for the External AE categories as outlined in Table 1.

5. Adverse event reports must be submitted promptly for any protocol deviations resulting in physical, psychological, social, or behavioral risks/harms of individual subjects or others who are enrolled in USU studies. This also must be reported as a protocol deviation. Refer to section 4.3 for the AE reporting timeline and format.

6. Failure of the PI to meet the AE reporting requirements will be referred to the IRB, Department Chairs, Institutional Official or the Office of the Under Secretary for Defense/Personnel and Readiness/Health Affairs for further action, which may include suspension of the study. For further information, please contact the AE reporting POC at each institution.

E. Adverse Event Report (AER) Form Separate templates are available on the DCI and USU IRB web site, denoted as Internal AER Form or External AER Form for reporting internal or external adverse events respectively. The appropriate form must be used when submitting the adverse event report. As appropriate, copies of pertinent pages from the subject's outpatient, inpatient medical records (to include medical summaries or autopsy reports), DSMB reports, hospital records, etc. should be submitted with the adverse event report to assist the IRB in their review of the event. All patient identifiers (name, patient ID number, address, and telephone number, etc.) must be eliminated or blocked from the copies of any medical records prior to the submission to the IRB

REPORTING OF INTERNAL OR EXTERNAL AEs TO THE IRB

	CRITERIA			REPORTING	
Category (C) (Physically or Psychologically)	Serious?	Unexpected?	Related or Possibly Related?	INTERNAL AE (from the time of the AE)	EXTERNAL AE (from the PI notification by the Sponsor)
Category- I (Prompt)	Yes Fatal Life-threatening All others	Yes*	Yes*	Within 48 hours Within 2 weeks Within 2 weeks	Within 48 hours Within 2 weeks Within 2 weeks
Category-2 (Prompt for Internal SAE or fatal External AE)	Yes Fatal Life-threatening All others	NO C	Yes*	Within 48 hours Within 2 weeks Within 2 weeks	Within 48 hours APR APR
Category-3 (Prompt for Internal SAE)	No	Yes*	Yes*	Within 2 weeks	APR
Category-4 (Prompt)	Any other adverse event that in the PI's opinion needs to be reported to the IRB			Within 2 weeks	Within 2 weeks
Category-5 (Prompt for Internal incident)	Unanticipated problems involving breach of confidentiality or HIPAA violation as defined in Section 4.5			Within 2 weeks	APR
Category-6 (Non-Prompt)	All Others			APRO	APR

a Use the Internal AER Form.
b Use the External AER Form.
c No-when there is no doubt. *Yes – includes "unsure" or "unknown" situation.
d APR-Annual Progress Report (APR) is during the continuing review of the protocol.

Serious AE (SAE):

1) Fatal (death).

2) Life-threatening

3) In-patient hospitalization or prolongation of existing hospitalization.

4) Persistent or significant disability/incapacity.

5) Congenital anomalies or birth defect.

6) Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subjects' health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).